University of Alberta

Three-Component Aza[4+2] Cycloaddition/Allylboration/Retro-sulfinyl-ene Approach to α-Hydroxyalkyl Piperidines and Palustrine Alkaloids

by

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of the

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LIST OF ABBREVIATIONS

9-BBN	9-borabicyclo[3.3.1]nonane
Ac	acetyl
Anal.	elemental Analysis
APT	attached proton test
Ar	aryl
Bn	benzyl
bs	broad singlet
Bu	butyl
Calcd	calculated
Cbz	carboxybenzoyl
CSA	10-camphorsulfonic acid
Cy	cyclohexyl
d	doublet
DA	Diels-Alder
DBA	*trans, trans* dibenzylideneacetone
de	diastereomeric excess
DIBAL-H	di-*i*-butylaluminum hydride
DIPEA	diisopropylethylamine
DMF	*N,N*-dimethylformamide
DOS	diversity-oriented synthesis
d.r.	diastereomeric ratio
EDG	electron donating group
EDDA	ethylenediammonium diacetate
ee	enantiomeric excess
EI	electron impact
equiv.	equivalents
er	enantiomeric ratio
ES	electrospray
Et	ethyl

Et_3N	triethyl amine
EWG	electron withdrawing group
FMO	frontier molecular orbitals
FTIR	fourier-transform infrared
FW	formula Weight
h	hour/hours
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Ipc	isopinocampheyl
IR	infrared
LUMO	lowest occupied molecular orbital
m	multiplet
MCR	multicomponent reaction
mCPBA	meta-chloro peroxybenzoic acid
Me	methyl
min	minute/minutes
MMPP	monoperoxyphtalate
MOM	methoxymethyl
m.p.	melting point
MS	mass spectrometry
NEDDA	normal electron demand Diels-Alder
NMR	nuclear magnetic resonance
Ns	nosyl
OTf	trifluoromethanesulfonate
Ph	phenyl
PMA	phosphomolybdic acid
PMB	4-methoxybenzyl
ppm	parts per million
Pr	propyl
q	quartet

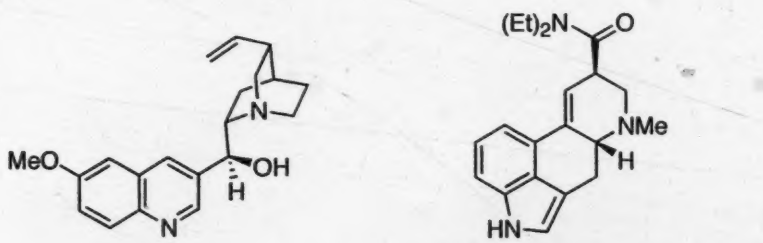
R	generic alkyl group
Red-Al	sodium [bis-(2-methoxyethoxy)] aluminun hydride)
RT	room temperature
s	singlet
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*t*-butyldimethylsilyl
TBDPS	*t*-butyldiphenylsilyl
THF	tetrahydrofuran
TFA	trifluoroacetic acid
TLC	thin layer chromatography
TOS	target-oriented synthesis
TMS	trimethylsilyl
UV	ultraviolet

Chapter 1

Introduction: Multicomponent Reactions (MCRs) and Diels-Alder Reactions in the Synthesis of Piperidine Motifs.

1.1 Introduction

The piperidine ring, perhaps, represents one the most ubiquitously distributed structural motif in Nature. For instance, quinine (**1**) and lysergic acid diethylamide (LSD) (**2**), two very famous compounds albeit for different reasons, share in common the presence of a piperidine unit (Figure 1.1).



1 quinine **2** lysergic acid diethylamide (LSD)

Figure 1.1. Example of biologically active compounds containing a piperidine ring.

Therefore, it is not surprising that immense synthetic efforts have been devoted to their syntheses. The applications of the Diels-Alder reaction have led the way for a long time, but the recent years have witnessed the emergence of multicomponent reactions (MCRs) as powerful synthetic strategies for the synthesis of piperidine natural products.

The elaboration of the piperidine structural unit via the above mentioned reaction strategies are summarized herein.

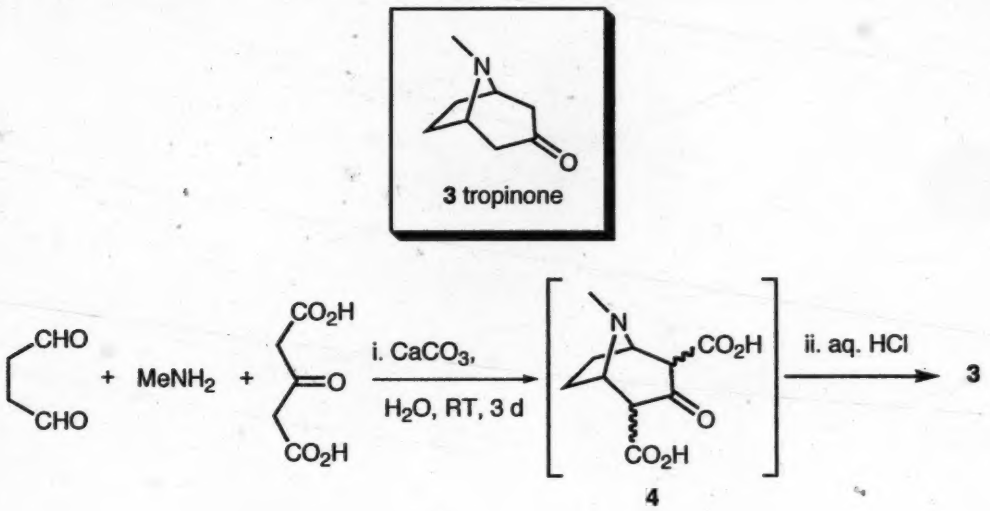
1.2 Multicomponent reactions (MCRs)

1.2.1 Background

The synthesis of urea by Wöhler constituted a landmark achievement as it laid the ground to the field of target-oriented organic synthesis.[1] Since then, significant progress has been achieved in this discipline; many powerful single bond forming reactions and asymmetric variants thereof have been developed. These discoveries have paved the way to the stereoselective assembly of complex organic molecules, a task deemed inconceivable by early practitioners. These successes, however, pale in comparison to the efficiency of Nature, which, served by millions of years of evolution, continues to inspire and challenge the synthetic community in their quest for more efficient chemical transformations. Indeed, nature has often been the catalyst behind many innovations in organic synthesis.[2] A recent trend in emulating its efficiency has consisted of merging compatible single bond forming processes as to allow multiple bond formation processes between several substrates, a concept named multicomponent reactions (MCRs).

In the present context, MCRs are broadly defined, regardless of their mechanistic nature, as "one-pot" processes that combine three or more substrates either simultaneously (so called "tandem" or "domino" reactions[3]), or through a sequential addition procedure that does not require any change of solvent. By saving synthetic operations while maximizing the buildup of structural and functional complexity, these highly step-economical reactions are particularly appealing in the context of target-

oriented synthesis. Although these advantages were demonstrated by Robinson as early as 1917, with the efficient one-step synthesis of the bridged bicyclic alkaloid tropinone **3** (Scheme 1.1),[4] MCRs have remained underexploited for many decades.

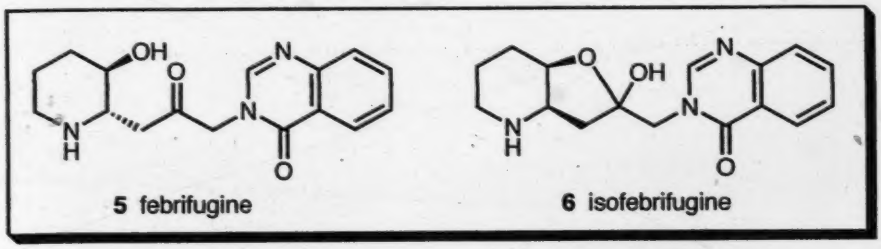


Scheme 1.1. Robinson's synthesis of tropinone

1.2.2 Synthesis of natural products containing piperidine motif via MCR strategies

The application of MCRs to the total synthesis of piperidine alkaloids will now be summarized. Due to space restrictions, most three-component reactions where one of the components is carbon monoxide (e.g. intermolecular Pauson-Khand reaction, or carbonylative cross-couplings) are not included.

1.2.2.1 Synthesis of febrifugine and isofebrifugine

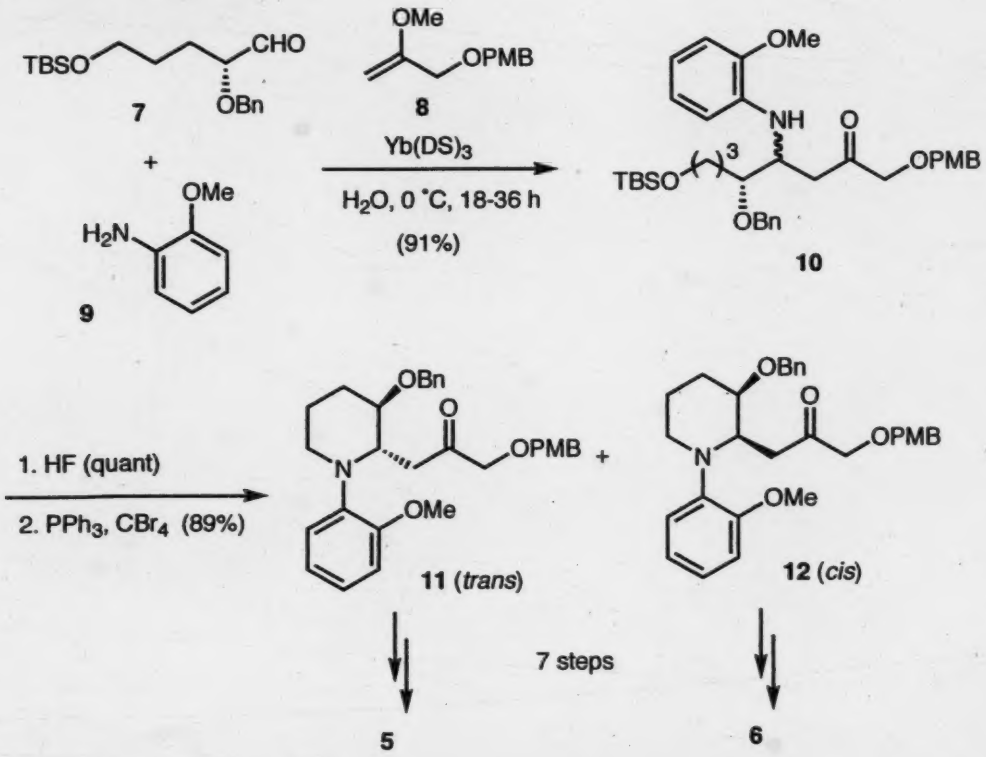


5 febrifugine **6** isofebrifugine

Figure 1.2. Febrifugine and isofebrifugine natural products

The intermolecular Mannich reaction combines an aldehyde, an amine and an enolizable carbonyl compound for the one-pot synthesis of β-amino ketones or esters.[5] Kobayashi and co-workers recently reported the asymmetric synthesis of the anti-malarial alkaloids febrifugine (**5**) and isofebrifugine (**6**) (Figure 1.2) utilizing this reaction process.[6] The required aldehyde precursor **7** was obtained through a Sn(II)-catalyzed asymmetric aldol reaction (Scheme 1.2).[7] The aldehyde was then mixed in one-pot with *o*-methoxyaniline **9** and the enol ether **8** to afford the key β-aminoketone **10** (2:1 d.r.) through a Mannich-type three-component reaction. This reaction was performed in an aqueous medium, and the use of a surfactant such as dodecyl sulfate ($Yb(DS)_3$) was found to be essential. The diastereomeric mixture **10** was treated with HF and the resulting primary alcohol was converted to the bromide, which underwent nucleophilic cyclization to afford piperidines **11** and **12**. These piperidines were then separated and independently elaborated in seven steps into **5** and **6**, the target molecules. The measured optical rotation of these compounds led to the conclusion that they were actually antipodes of the natural products. A similar synthetic sequence led to the synthesis of the

corresponding enantiomers, which were shown to have optical rotation identical to the respective natural products.



Scheme 1.2. A Mannich-type three-component reaction approach to febrifugine and isofebrifugine by Kobayashi and co-coworkers.

1.2.2.2 Synthesis of martinelline

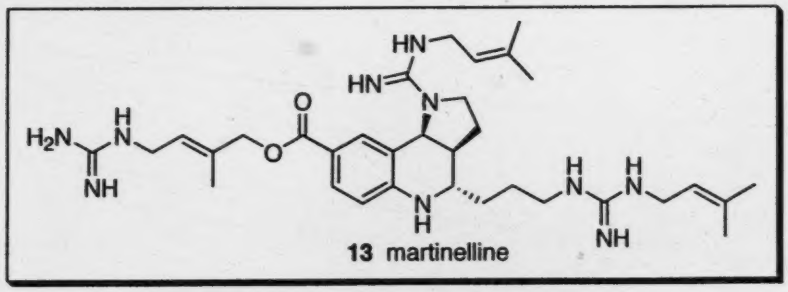
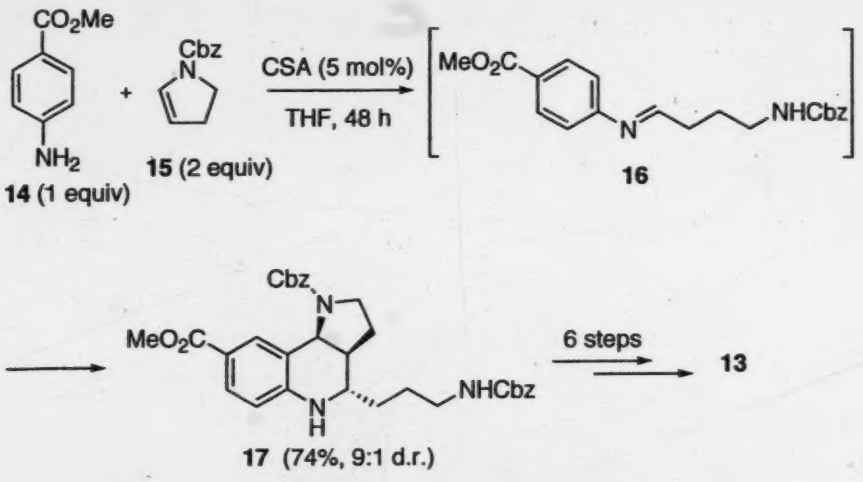


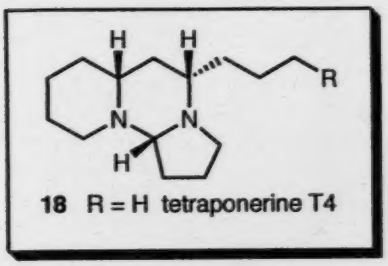
Figure 1.3. Structure of martinelline

The antibiotic and G-protein coupled receptor (GCPR) ligand martinelline (**13**, Figure 1.3) is a hydroquinoline alkaloid that was first isolated from the root extracts of the *Martinella iquitosensis*.[8] The retrosynthesis of this compound by Batey and co-workers[9] recognized that the unprecedented hexahydropyrrolo[3,2-*c*]quinoline core could be synthesized using a three-component Pavarov hetero Diels-Alder reaction.[10] However, for this synthetic strategy to be successful, reaction conditions favoring the approach of the dienophile in an *exo* over the *endo* fashion had to be found. For this purpose, a variety of protic acids were investigated, and it was found that the reaction was best carried out in the presence of camphorsulfonic acid (CSA). To this end, a mixture of 4-aminobenzoate **14** and *N*-Cbz-2-pyrroline **15** were stirred at room temperature in the presence of catalytic CSA to afford the *exo* cyclo-adduct **17** as the major product (Scheme 1.3). The *N*-Cbz-2-pyrroline served both as an aldehyde equivalent and a dienophile in this context. The Diels-Alder adduct **17** bore all the requisite functionalities for the successful completion of the synthesis, which was achieved in six additional steps.

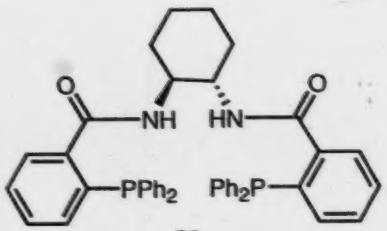


Scheme 1.3. Synthesis of martinelline by Batey and co-workers.

1.2.2.3 Synthesis of tetraponerines



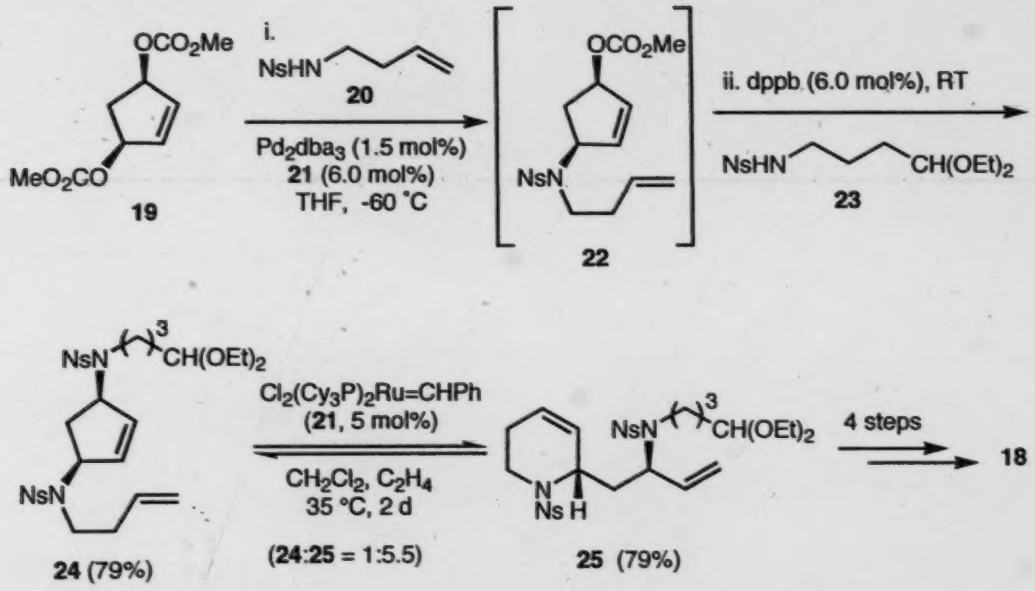
18 R = H tetraponerine T4



21

Figure 1.4. General motif of tetraponerines and structure of the Trost's chiral diphosphine

Symmetrically substituted cyclopentenes have proven to be very good substrates for use in allylic substitution chemistry.[11] This chemistry has been elegantly exploited by Blechert and co-workers for the synthesis of the nerve poisoning tetraponerine natural products, such as **18** (Figure 1.4).[12] This natural product was first isolated from the New Guinean ant *Tetraponera sp.*[13] The synthesis of **18** began with the desymmetrization of dicarbonate **19**, initiated by the addition of one equivalent of *N*–(3-butenyl)nosylamide **20** under palladium catalysis in the presence of Trost's chiral diphosphine ligand **21** (Scheme 1.4). When the first allylic substitution was complete, the reaction was allowed to warm up and the intermediate **22** was treated *in situ* with one equivalent of a second nosylamide (**23**). The product **24** resulting from this double substitution reaction mixture was subjected to a tandem intramolecular ROM/RCM to furnish the key precursor **25**, which was engaged in the final cyclization step by the reduction of the double bonds, followed by the HCl-promoted domino deprotection of the acetal and aminal formation.



Scheme 1.4. Three-component allylic substitution approach to tetraponerine alkaloids by Blechert and co-worker.

1.2.2.4 Synthesis of emetine

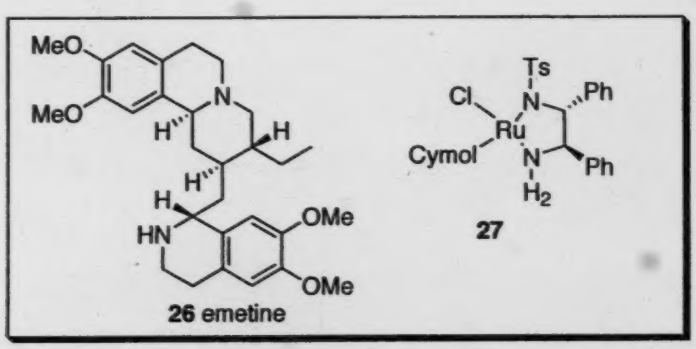
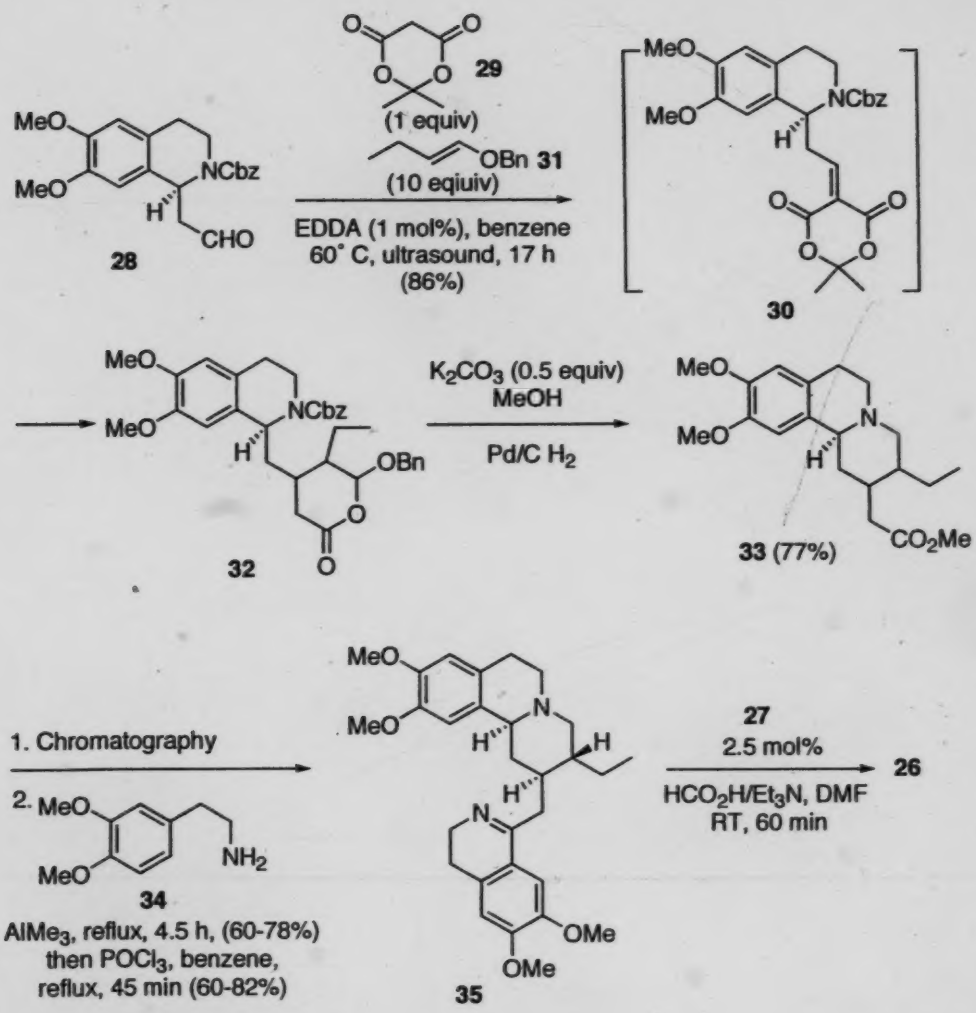


Figure 1.5. Structure of emetine **26** and Noyori's hydrogenation catalyst **27**.

Tietze and co-workers used a powerful three-component domino Knoevenagel condensation/hetero[4+2] reaction sequence towards the preparation of the naturally

occurring isoquinoline called emetine (**26**, Figure 1.5).[14] Emetine is the main alkaloid found in the root of *Cephaelis ipecacuanha*,[15] and it has been used for centuries as an emetic. Subsequently it has been shown to be a potent antiamebic.[16] The MCR was initiated by a Knoevenagel condensation between aldehyde **28** and Meldrum's acid **29** to afford *in situ* a 1-oxabutadiene **30**, which undergoes a Diels-Alder reaction with enol ether **31**. The resulting cycloadduct is unstable under the reaction conditions and loses acetone via a formal retro[4+2] process to afford lactone **32** (Scheme 1.5). A Pd(0) catalyzed debenzylation in methanol prepared the stage for a skeletal rearrangement, which culminated in the formation of ester **33**. Further elaboration of the latter via a Bischler–Napieralski reaction and Noyori's asymmetric transfer hydrogenation using catalyst **27**[17] led to emetine (**26**). A similar route was also applied to a small library of isoquinolines of this class.



Scheme 1.5. A tandem Knoevenagel condensation/hetero[4+2] route to emetine by Tietze and co-workers.

1.2.2.5 Synthesis of dendrobatid alkaloid 251F

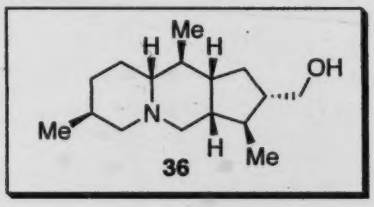
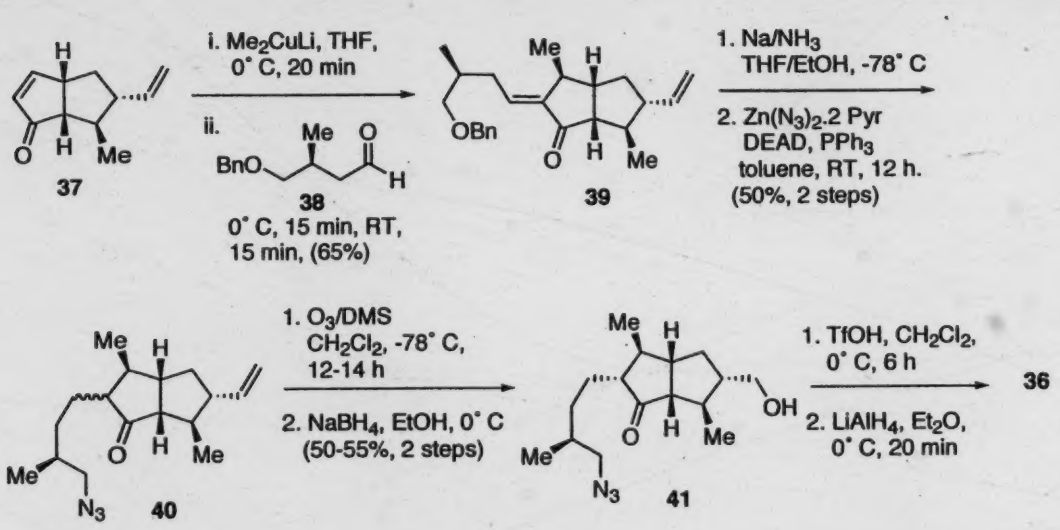


Figure 1.6. Structure of the dendrobatid alkaloid 251F.

The dendrobatid alkaloid 251F (**36**, Figure 1.6) was isolated from the skin exudates of a Colombian dendrobatid poison frog, *Minyobates bombetes*.[18] Aubé and coworkers recently reported the asymmetric total synthesis of this molecule (Scheme 1.6).[19] The bicyclic enone **37** was prepared via a tandem ROM/RCM reaction and subjected to Noyori-type three-component reaction conditions to afford the advanced bicyclopentenone intermediate **39**. The latter was first converted to the key Schmidt rearrangement precursor **40**, which was carried through an ozonolysis and reduction reaction sequence. The resulting product **41** was then treated with triflic acid to promote the Schmidt rearrangement, followed by $LiAlH_4$ reduction of the resulting lactam to afford the natural product **36**.



Scheme 1.6. Noyori-type three-component approach to dendrobatid alkaloid 251F by Aubé and co-workers.

It is clear from the variety of piperidine natural products described in this chapter that MCRs demonstrate a wide scope of applications. The development of new MCRs constantly opens up new opportunities, and it is likely that the application of these powerful processes to natural product synthesis is only in its infancy. Appealing characteristics of MCR such as convergence and step-economy are also shared by the Diels-Alder reaction. Its applications to the synthesis of the piperidine motif will be discussed next.

1.3 The Diels-Alder reaction

The Diels-Alder reaction (DA), first described in 1928,[20] represents one of the most powerful strategies for the construction of six-membered carbocycles and heterocycles. This efficient $4_{\pi}+2_{\pi}$ electron cycloaddition reaction has been the focus of

extensive mechanistic studies, primarily driven by its enormous synthetic potential.[21] These initial efforts paved the way to the theory of conservation of orbital symmetry, which has shaped our fundamental understanding of this reaction and many other pericyclic processes. Indeed, inspired by the frontier molecular orbital theory (FMO),[22] Woodward and Hoffman introduced the theory of the conservation of orbital symmetry to explain some features of the DA reaction (*vide infra*).[23] It followed that three different classes of DA reaction can be distinguished on the basis of the dominant interaction in the transition state (Figure 1.7). The first type involves the $HOMO_{diene}/LUMO_{dienophile}$-controlled [4+2]-cycloaddition processes, also called normal electron demand DA (NEDDA). Those cycloadditions represent the first cases reported by Otto Diels and Kurt Alder.[20] The vast majority of reported DA reactions operate via this type of orbital interaction, whereby the diene typically bears at least one electron releasing group while its cycloaddition partner is an electron deficient dienophile. The second type of DA reaction, the $HOMO_{dienophile}/LUMO_{diene}$-controlled processes also called Inverse Electron Demand DA (IEDDA), has been extensively documented over the last three decades.[24] Those types of DA reaction can sometimes proceed under milder reaction conditions than their NED counterparts, although they are less commonly used. In sharp contrast, examples of the third type of DA, which involves unactivated dienes and dienophiles, have been scarce. Those reactions require forcing conditions, such as the use of high temperature and/or pressure, and transition metal catalysis. Although in the latter case, the reaction may proceed via a different mechanism.

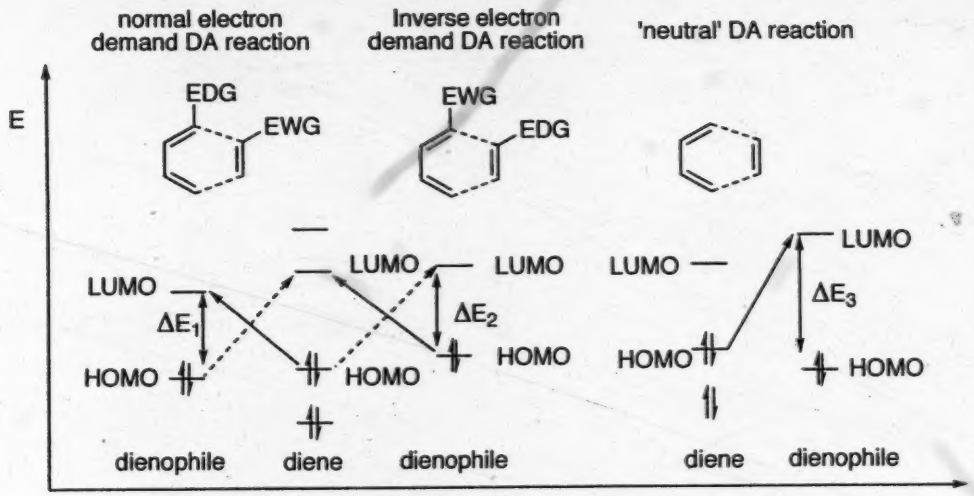
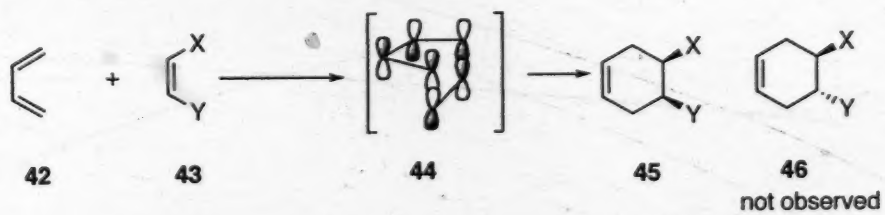


Figure 1.7. Classes of DA reactions with energy profile.

Unlike the third type of DA reaction, the first and second types share in common a high degree of regio- and stereoselectivity in the carbon-carbon bond forming process. These interesting features as well as the reactivity of the reaction components can be rationalized using FMO theory.

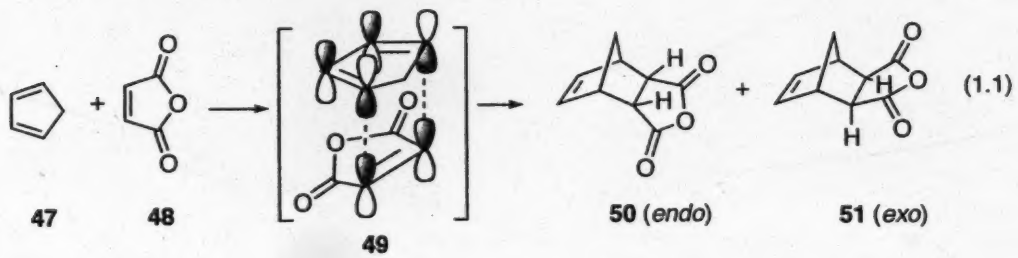
1.3.1 Stereochemical outcome rationale

One of the interesting feature of the Diels-Alder reaction is its stereospecific nature, which mainly stems from the high *syn* (suprafacial) addition with respect to both the diene and the dienophile (Scheme 1.7).[25]



Scheme 1.7. Stereochemical rationale of the DA reaction

It is also noteworthy that the DA reaction predominantly yields the *endo* product **50** over the *exo* product **51** (Equation 1.1), although the latter is typically thermodynamically more stable (The Alder "endo rule").[26]



(1.1)

Indeed, the conversion of the *endo* adduct to the *exo* one via a retro-DA has been documented.[27] Woodward and Hoffman have shed light on this surprising preferential formation of the *endo* product using FMO theory. They pointed out that, in addition to the dominant (primary) interaction, *secondary* orbital interactions can occur in the *endo* approach (Figure 1.8). As a result, the energy of the transition state of the *endo* approach of the dienophile with respect to the diene is significantly lowered. Such a *secondary* orbital interaction does not exist in the *exo* transition state.

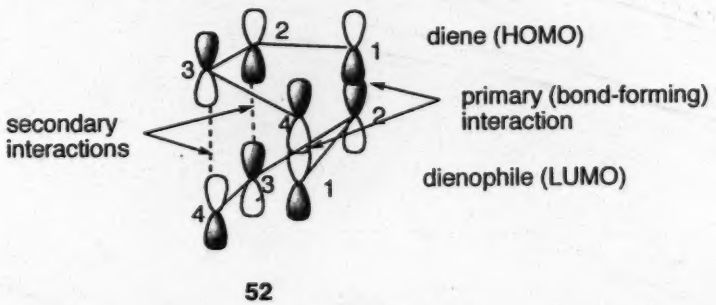
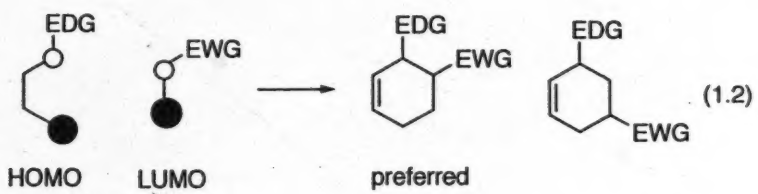


Figure 1.8. Picture of orbital interaction in the *endo* transition state.

1.3.2 The regiochemistry rationale

Atomic coefficients determined by the FMO computational model have helped predict the regiochemical outcome of the reaction. The regiochemistry of the DA reaction is indeed sensitive to the nature of substituents on the reactants. When unsymmetrical dienes and dienophiles are used, the regiochemistry of the major cycloadduct can be understood on the basis of the atomic orbital coefficients.[28] It follows that the major isomer would result from connecting the atoms with the largest coefficients in the frontier orbital of the two components, (Eqation 1.2).



1.3.3 Reactivity trend

As illustrated in Figure 1.7, the energy value of the frontier molecular orbitals is largely influenced by the nature of the substituents on both the diene and the dienophile. These energies can be estimated using the FMO method, and usually provide insight into the reactivity of the reaction components. This prediction method is, however, only appropriately applied to reactions that proceed on the NED manifold.[29] In general, electron-donating groups (EDG) are known to increase the energy of the HOMO, and the electron withdrawing groups (EWG) decrease the energy of the LUMO. The net

combined effect is the reduction of the energy gap between the two sets of orbitals, which translates into higher reactivity.

The reaction can further be accelerated by use of Lewis acids.[30a] In some cases, the Lewis acid catalysis allows reactions that otherwise would have been very difficult, if not impossible, to proceed under mild conditions. This finding has also paved the way to the development of catalytic asymmetric cycloadditions.[30b]

In addition to the effect of the substituents, the DA reaction, although concerted, is sensitive to steric factors in some cases. This is more noticeable in acyclic 1,4-substituted dienes, as the equilibrium would favor the *s-trans* **53** rather than the reactive *s-cis* **54** conformation, (Figure 1.9). For this reason, dienes that are constrained to a *s-cis* conformation are typically more reactive.

53 (*E, Z*) **54** (*Z,Z*)

Figure 1.9. Effect of diene conformation

1.4 Construction of piperidines via a DA reaction strategy

The vast majority of Diels-Alder reaction approaches to piperidines employs activatived imines as dienophiles, (Figure 1.10). The EWG mainly serves the purpose of lowering the energy of the $LUMO_{dienophile}$, thereby allowing the reaction to occur under mild conditions. However, Lewis acid catalysis has recently allowed the use of simpler unactivated imines and catalytic asymmetric variants have now been reported.[30,31]

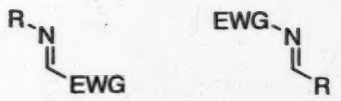
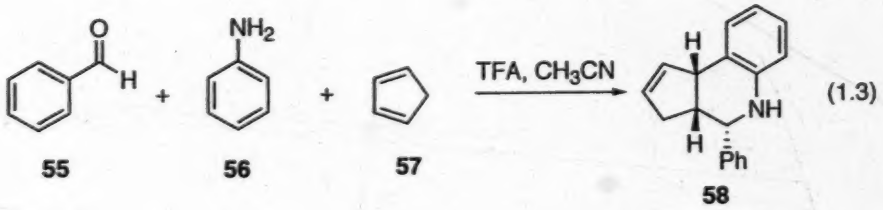


Figure 1.10. Activated imine dienophiles.

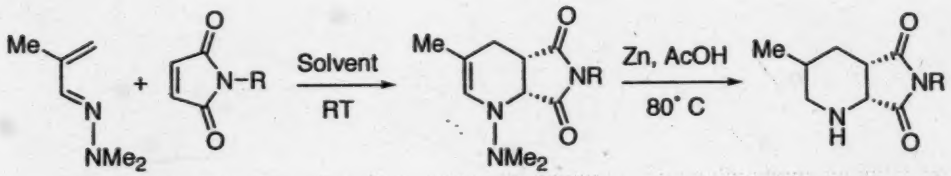
The application of the opposite synthetic stratagem utilizing 1-aza-dienes has rarely been reported. Indeed, simple α,β-unsaturated imines suffered low conversion, competitive imine addition and/or isomerization problems. In addition, the enamine reaction products are unstable. Examples with these type of dienes, however do exist, notably the Grieco three-component reaction (Equation 1.3),[32] a variant of the Pavarov reaction[10] whereby the imine is generated *in situ*.



In addition to the above cases, Fowler and co-workers have demonstrated that 1-acyl-aza-dienes can be used in DA reaction, although the scope seemed limited to the intramolecular variant.[33] Subsequently, Boger and co-workers have demonstrated that *N*-sulfonyl-1-aza-1,3-butadienes undergo intermolecular Diels-Alder to afford highly decorated piperidines.[34]

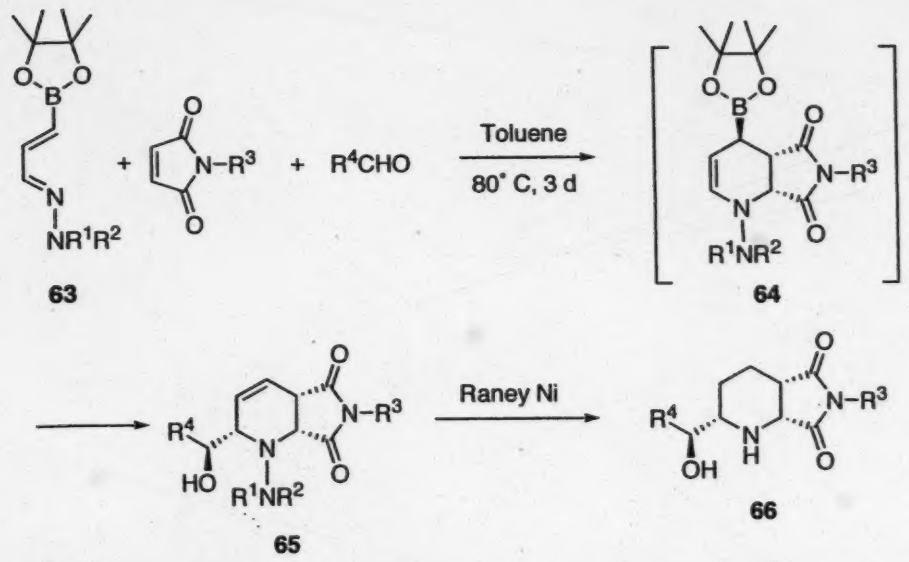
Ghosez and coworkers reasoned that the use of hydrazines in place of amines with unsaturated aldehydes would make electron-rich 1-aza-dienes, and thus expand the

reaction scope. As a proof of concept, hydrazonodiene **59** was reacted with maleimides and maleic anhydride to afford bicyclic piperidine precursors in good yield, (Scheme 1.8). Mono-activated dienophiles could also be used, although forcing reaction conditions were required.[35] The use of chiral hydrazines has allowed the development of an efficient asymmetric variant.[36]



Scheme 1.8. Use of 1-dialkylamino-1-aza-diene in the DA reaction by Ghosez and co-workers.

This synthetic strategy was also elegantly exploited by Hall and Tailor to access α-hydroxyalkyl piperidines, (Scheme 1.9).[37] In this event, the hydrazonodiene **63** together with various maleimides and aldehydes were heated in toluene to afford a single diastereomer of *N*-amino piperidines **65**. The latter compound was then converted to piperidine **66** by simple treatment with Raney nickel under a high pressure of hydrogen. This process is the precursor of this thesis. The α-hydroxyalkyl piperidine structural motif is encountered in piperidine alkaloids of interest. Thus, it may be beneficial to briefly discuss the key strategy that has allowed the introduction of the α-hydroxyalkyl side chain, namely the allylboration reaction.



Scheme 1.9. Tandem aza[4+2]/allylboration route to piperidines by Hall and Tailor.

1.5 Allylboration

1.5.1 Overview

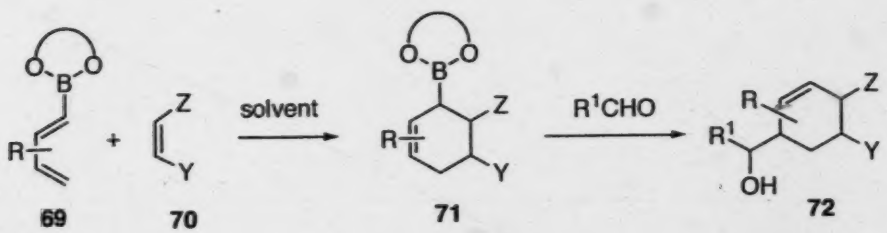
The allylation reaction represents one of the most efficient strategies for the generation of homoallylic alcohols **68**, which constitute a very useful class of intermediates in organic synthesis.[38] Allylboranes and allylboronates have been classified as Type I allyl transfer reagents,[39] as the reaction is believed to proceed via a six-membered transition state **67** with boron also serving the role of an internal Lewis acid (Figure 1.11).[40]

Figure 1.11. The allylboration reaction

This mechanistic insight has led to the design of various boron allylation systems and asymmetric variants thereof. The use of chiral allylboranes, and allylboronates, championed by Brown and Roush respectively have set the standard for a long time.[41] However the former compounds are extremely reactive and highly sensitive to moisture, while the latter are air sensitive and afford low enantioselectivity for γ-substituted reagents. In an attempt to address some of these issues, Batey and co-workers have recently introduced an air and moisture stable trifluoroallylborate allylating reagent, although an asymmetric variant still awaits.[42] The most promising result in term of stability came recently from an investigation by our laboratory on allylpinacolate reagents.[43] These compounds share the same air and moisture stability features as the trifluroallylborate reagents, however their widespread use was hampered by their inherent low reactivity. Hall and Kennedy demonstrated that the reaction of various allylpinacolates with aldehydes, which are notoriously slow, can be accelerated through the use of an external Lewis acid with no apparent loss of stereospecificity. In the event, it was found that scandium and copper (II) triflate best served the purpose. Moreover, the reaction also proceeded at low temperatures, a feature that subsequently led to the development of a highly practical asymmetric allylboration and crotylboration system based on camphordiol boraonates.[44] The reaction is believed to proceed *via* electrophilic activation of the dioxaborolane in a closed transition state.[45] Shortly thereafter, Miyaura and co-workers also disclosed a similar strategy, although in this case a chiral metal catalyst was exploited, and moderate enantiomeric excesses were observed.[46]

1.5.2 Cyclic Allylboronates

The use of this class of constrained reagent, whereby the allyl moiety is embedded within a ring system, is rare. This is most likely due to the difficulty in their preparation. One approach to this type of compound based on a rhodium promoted hydroboration of cyclohexadiene has been reported.[47] However, the limited supply of this type of precursor severely limits their applications. Another useful strategy has been disclosed by Vaultier and co-workers (Scheme 1.10), who demonstrated that the desired allylboronates **71** could be accessed *via* a DA reaction between 1-borono-1,3-butadienes **69** and appropriate electron deficient dienophiles **70**. The intermediates **71** were then allowed to react with an aldehyde to afford the α-hydroxyalkyl cyclohexadienes **72**.[48] It was also demonstrated that this entire sequence could be carried out in one-pot, thereby avoiding the need to isolate the allylboronate intermediate.[49]



69 **70** **71** **72**

Scheme 1.10. DA reaction approach to cyclohexenylboronates by Vaultier and co-workers.

A similar reaction strategy was used by Hall and Tailor to access α-hydroxyalkyl piperidines.[37] Subsequently, this type of reaction strategy has been utilized by Hall and Gao[50] as well as Carboni and co-workers[51] to access tetrahydropyran derivatives.

1.6 Goal of the Project

The α-hydroxyalkyl piperidine motif is frequently encountered in nature, and some representative natural products containing this motif are depicted in Figure 1.12.

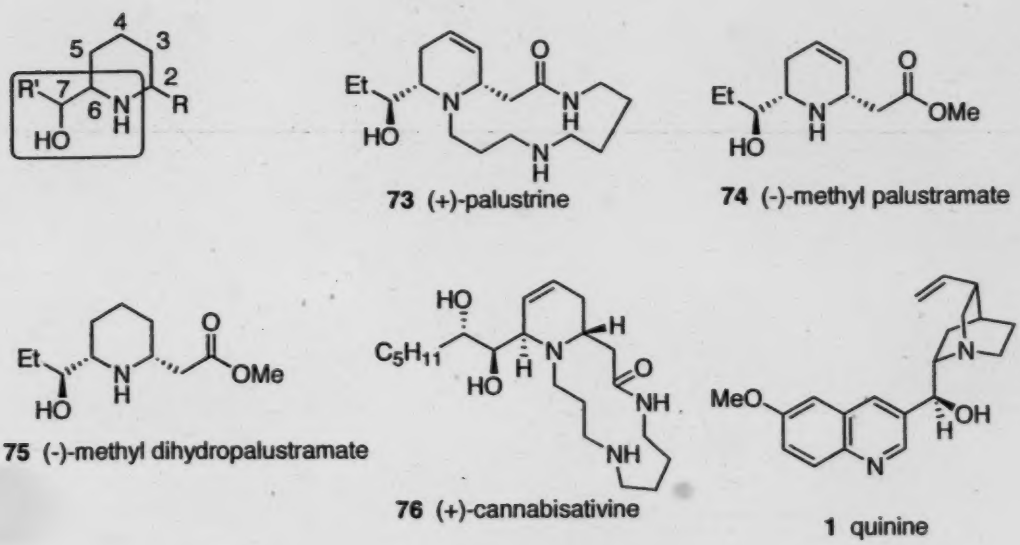


Figure 1.12. Selected α-hydroxyalkyl piperidine containing natural products.

These alkaloids have captured the imagination of the synthetic community for a long time because of their biological activity and also the challenge of the stereoselective construction of the core α-hydroxyalkyl piperidine unit. Previous syntheses of this motif (to be discussed in Chapter 4), have relied on tedious linear synthetic manipulations. In

an attempt to address this issue, a one step stereocontrolled construction approach to α-hydroxyalkyl piperidines was reported by Hall and Tailor (Scheme 1.9).[37] An additional appeal of this methodology is its potential applications in diversity oriented synthesis. However, although a wide variety of aldehyde and hydrazine were tolerated in this reaction, the intrinsic low reactivity of the pinacol boronic ester dienes only allowed the use of maleimide derivatives as dienophiles. As a consequence, only 2,4,5-trisubstituted piperidines were obtained as products. Unfortunately, this pattern of substitution is not observed in any known natural product. As such, at that time the scope of the reaction was limited to diversity-oriented synthesis applications. In addition, the synthesis of **58**, the key diene component was also very difficult and low yielding.

In order to harness the synthetic potential of this tandem DA/allylboration reaction, we reasoned that it was essential to first explore avenues leading to an increase of the diene's reactivity. Ideally, the new dienes would undergo a Diels-Alder reaction with mono-activated dienophiles. The 2-substituted products of such reactions would closely resemble some of the natural products shown in Figure 1.12.

Our ultimate goal remained the application of this methodology in total synthesis, which could alternatively be accomplished through the use of di-activated dienophiles. These dienophiles would have to satisfy the following requirements:

1. Possess the requisite electronic characteristics to react with heterodienes.
2. Provide high enantiofacial selectivity.
3. Lead to a cycloadduct convertible to both C3-C4 or C4-C5 dehydro compounds, a condition essential for the synthesis of palustrine (**73**) and cannabisativine (**76**) family members and the corresponding saturated series.

The three-component aza[4+2]/allylboration reaction initially developed in our laboratory also relied on the use of 1-diakylamino-1-aza dienes, which delivered products that can not be further elaborated into alkoids bearing unsaturations such as palustrine (**73**). Indeed, despite the wide potential synthetic applications of this process the chemoselective cleavage of tetraalkylhydrazines in the presence of unsaturations was unprecedented. Our approach to some of the natural products shown previously would require the development of such a new synthetic methodology.

1.7 References

(1) Wöhler, F. *Ann. Phys. Chem.* **1928**, *12*, 253.

(2) (a) Deslongchamps, P. *Aldrichimica Acta* **1984**, *17*, 59. (b) Ho, T.-L.; *Tactics of Organic Synthesis*, Wiley-Interscience 1994. (c) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551-564.

(3) Tietze, L.F. *Chem. Rev.* **1996**, *96*, 115-136.

(4) Robinson, R. *J. Chem. Soc.* **1917**, 762-768.

(5) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem. Int. Ed.* **1998**, *37*, 1044-1070

(6) Kobayashi, S.; Ueno, M.; Suzuki, R.; Ishitani, H.; Kim, H-S.; Wataya, Y. *J. Org. Chem.* **1999**, *64*, 6833-6841.

(7) (a) Kobayashi, S.; Hayashi, T. *J. Org. Chem.* **1995**, *60*, 1098-1099. (b) Kobayashi, S.; Horibe, M. *Chem. Eur. J.* **1997**, *3*, 1472-1481.

(8) Gentry, A. H.; Cook, K. *J. Ethnopharmacol.* **1984**, *11*, 337-334

(9) Powell, D. A.; Batey, R. A. *Org. Lett.* **2002**, *4*, 2913-2916.

(10) Povarov, L. S. *Russ. Chem. Rev.* **1967**, *36*, 656.

(11) (a) Trost, B. M.; Lee, C. *Catalytic Asymmetric Synthesis*, Ojima I., Ed.; 2nd Ed.; Wiley-VCH: New York, 2000, 593-649. (b) Graening, T.; Schmalz, H. –G.; *Ang. Chem. Int. Ed.* **2003**, *42*, 2580-2584.

(12) Stragies, R.; Blechert, S. *J. Am. Chem. Soc.* **2000**, *122*, 9584-9591.

(13) Braekman, J.C.; Daloze, D.; Pasteels, J. M.; Van Hecke, P.; Declercq, J. M.; Sinnwell, V.; Francke, W. Z. *Naturforsch* **1987**, *42c*, 627-630

(14) Tietze, L. F.; Rackelmann, N.; Sekar, G. *Angew. Chem. Int. Ed.* **2003**, *42*, 4254-4257.

(15) Mahran, G. H.; Hilal, S. H.; Elalfy, T. S. *Planta Med.* **1975**, *27*, 127-132.

(16) Fujii, T.; Ohba, M. *The Alkaloids* **1989**, *22*, 1.

(17) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916 – 4917.

(18) Spande, T. F.; Garraffo, H. M.; Yeh, H. J. C.; Pu, Q. –L.; Pannell, L. K.; Daly, J. W. *J. Nat. Prod.* **1992**, *55*, 707-722.

(19) Wrobleski, A.; Sahasrabudhe, K. J. Aubé, *J. Am. Chem. Soc.* **2002**, *124*, 9974-9975.

(20) Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1928**, *460*, 98-122.

(21) (a) Nicolaou, K. C. ; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed.* **2002**, *41*, 1648-1678. (b) Corey, E. J. *Angew. Chem. Int. Ed.* **2002**, *41*, 1650-1667.

(22) Fukui, K. *Acc. Chem. Res.* **1981**, *14*, 363-368.

(23) Hoffmann, R.; Woodward, R. B. *J. Am. Chem. Soc.* **1965**, *87*, 4388-4389.

(24) For reviews of inverse electron demand Diels-Alder reactions, see: (a) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869-2939. (b) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781-794. (c) Boger, D. L.; Weinreb, S. N. In *Hetero Diels-Alder Methodology in Organic Synthesis*; Wasserman, H. H., Ed.; Academic: New York, 1987; Vol. 47, Chapters 9 and 10. (d) Boger, D. L.; Patel, M. *Prog. Heterocycl. Chem.* **1989**, *1*, 30-64. (e) Kametani, T.; Hibino. S. *Advances in Heterocyclic Chemistry*, Katritzky, A. R., Ed.; Academic: New York, 1987; Vol. 42, pp 245-333. (f) Boger, D. L. *Chemtracts: Org. Chem.* **1996**, *9*, 149-189. (g) Boger, D. L. *Bull. Chim. Soc. Belg.* **1990**, *99*, 599-615. (h) Boger, D. L. *J. Heterocycl. Chem.* **1996**, *33*, 1519-1531. (i) Boger, D. L. *J. Heterocycl. Chem.* **1998**, *35*, 1001-1011.

(25) Houk, K. N.; Lin, Y. -T.; Brown, F. K. *J. Am. Chem. Soc.* **1986**, *108*, 554-556.

(26) Alder, K.; Stein, G. *Angew. Chem.* **1937**, *50*, 510.

(27) (a) Wasserman, A. *Diels-Alder Reactions*, Elsevier Publishing Co.: New York, 1965. (b) Berson, J. A.; Mueller, W. A. *J. Am. Chem. Soc.* **1961**, *83*, 4947-4947.

(28) Mohler, D. L.; Vollhardt, K. P. C.; Wolff, S. *Angew. Chem. Int. Ed.* **1990**, *29*, 1151-1154.

(29) Spino, C.; Rezaei, H.; Dory, Y. L. *J. Org. Chem.* **2004**, *69*, 757-764.

(30) (a) Yates, P., Eaton, P. *J. Am. Chem. Soc.* **1960**, *82*, 4436-4437. (b) Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3558-3500.

(31) Laschat, S.; Dickner, T. *Synthesis* **2000**, *13*, 1781-1813.

(32) Grieco, P. A.; Bahsas, A. *Tetrahedron Lett.* **1988**, *29*, 5855-5858

(33) (a) Cheng, Y. -S.; Fowler, F. W.; Lupo, A. T., Jr. *J. Am. Chem. Soc.* **1981**, *103*, 2090-2091. (b) Cheng, Y. -S.; Lupo, A. T., Jr.; Fowler, F. W. *J. Am. Chem. Soc.* **1983**, *105*, 7696-7703. (c) Hwang, Y. C.; Fowler, F. W. *J. Org. Chem.* **1985**, *50*, 2719-2726.

(34) Boger, D. L.; Corbett, W. L.; Curran, T. T.; Kasper, A. M. *J. Am. Chem. Soc.* **1991**, *113*, 1713-1729.

(35) Serckx-Poncin, B.; Hesbain-Frisque, A. -M.; Ghosez, L. *Tetrahedron Lett.* **1982**, *32*, 3261-3264

(36) Beaudegnies, R.; Ghosez, L. *Tetrahedron Asymm.* **1994**, *5*, 557-560.

(37) Taylor, J.; Hall, D. G. *Org. Lett.* **1999**, *2*, 3715-3718.

(38) For reviews, see: (a) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, **2000**; Chapter 10, 299-402.

(39) Denmark, S. E.; Weber, E. J. *Helv. Chim. Acta* **1983**, *66*, 1655-1660.

(40) Li, Y.; Houk, K. N. *J. Am. Chem. Soc.* **1989**, *111*, 1236-1240.

(41) For reviews see: (a) Chemler, S. R.; Roush, W. R. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 11, 403-490. (b) Hall, D. G.; Kennedy, J. W. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 4732-4739.

(42) Batey, R. A.; Thadani, A. N.; Lough, A. J. *J. Am. Chem. Soc.* **1999**, *121*, 450-451.

(43) Hall, D. G.; Kennedy, J. W. J. *J. Am. Chem. Soc.* **2002**, *124*, 11586-11587.

(44) Lachance, H.; Lu, X.; Gravel, M.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 10160-10161.

(45) Rauniyar, V.; Hall, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 4518-4519.

(46) Ishiyama, T.; Ahito, T. A.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 12414-12415.

(47) Satoh, M.; Nomoto, Y.; Miyaura, N.; Suzuki, A. *Tetrahedron Lett.* **1989**, *30*, 3789-3792.

(48) Vaultier, M.; Truchet, F.; Carboni, B.; Hoffmann, R. W.; Denne, I. *Tetrahedron Lett.* **1987**, *28*, 4169-4172.

(49) Six, Y.; Lallemand, J-Y. *Tetrahedron* **1999**, *40*, 1295-1296

(50) Gao, X.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 9308-9309.

(51) Deligny, M.; Carreaux, F.; Carboni, B.; Toupet, L.; Dujardin, D. *Chem. Commun.* **2003**, 276-277.

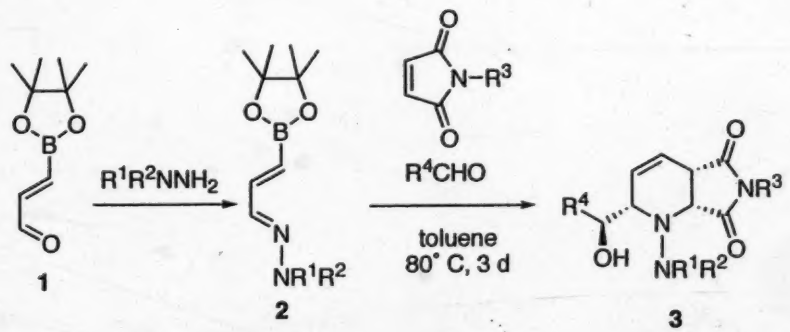
Chapter 2

A Practical Route to Alkenylboronates via their Boronic Acid Precursors

2.1 Background

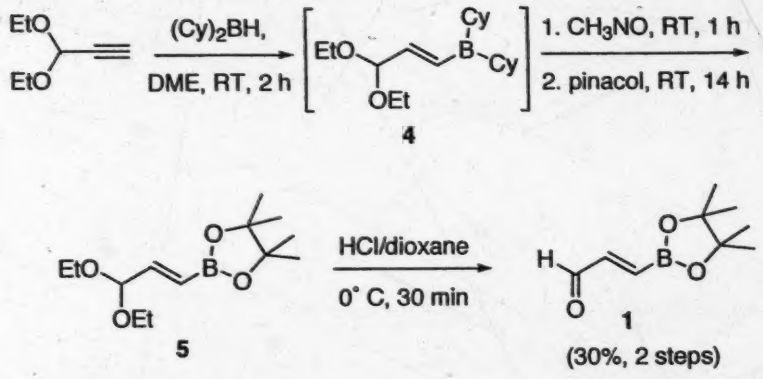
The hydroboration reaction was first reported by Brown and Subba Rao almost half a century ago.[1] Since then, it has established itself as the standard method for the synthesis of (*E*)-1-alkenyl and alkylboronic acid derivatives. This discovery marked the beginning of a flourishing era in the field of organoborane chemistry, which has now become an important area of synthetic chemistry. For instance, the Suzuki-Miyaura cross-coupling[2] reaction is now routinely used in the elaboration of complex targets both in academia and in industry.[3,4] Other important boron-based reactions include the borono-Mannich reaction,[5] the rhodium(I)-catalyzed addition of boronic acids to aldehydes,[6,7] alkenes,[8,9] and copper diacetate-promoted cross-coupling reactions involving amines,[10] alcohols,[10] and thiols[11]. Both aryl- and alkenylboronic acids can participate in these reactions; however, the challenge posed by the isolation of the latter class of compounds has significantly hampered their use. Indeed, most alkenylboronic acids are unstable under conventional purification conditions and their corresponding esters, although stable, are not suitable for some of the above synthetic applications.[5-11]

The Vaultier three-component reaction[12] and the aza-variant extension developed by our laboratory[13] also demonstrate the utility of boron compounds in organic synthesis (Scheme 2.1.).



Scheme 2.1. The aza[4+2]cycloaddition/allylboration three-component approach to α-hydroxyalkyl piperidine

In the latter case, the key borono-acrolein reaction component **1** was initially obtained via hydroboration of the propiolaldehyde diethyl acetal precursor with dicyclohexylborane, followed by oxidation using trimethylamine-*N*-oxide (TMAO), transesterification using pinacol and deprotection of the acetal (Scheme 2.2).[13a,14] The product **1** could be obtained in pure form after two distillations, which were required to remove the cyclohexanol by-product, albeit in low yield due to extensive decomposition during this operation.



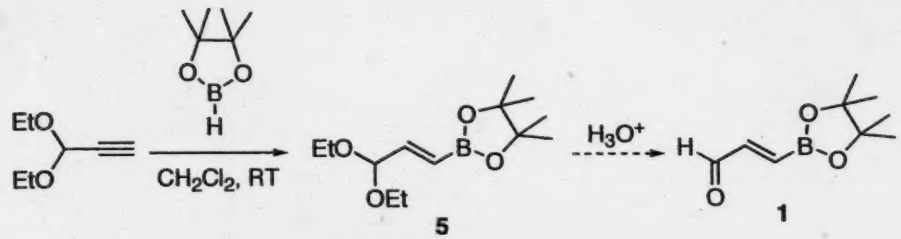
Scheme 2.2. Previous route to 3-borono-acrolein pinacolate (**1**)

This example typifies the difficulties associated with the purification of boron containing compounds. As one of our objectives was the exploration of the full potential of the hetero[4+2]/allylboration three-component reaction described above, the efficient preparation of boronate **1**, became the focus of our initial efforts.

2.2 Results and Discussion

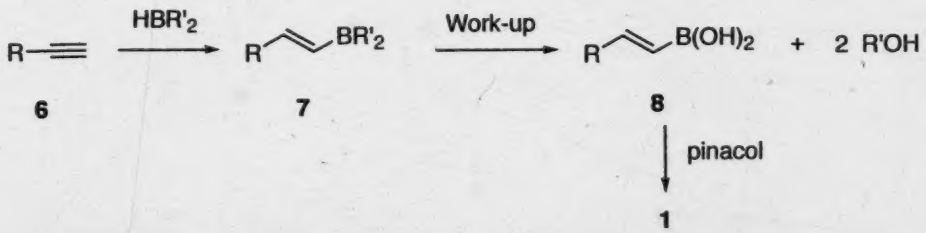
2.2.1 Pinacolborane hydroboration route to boronate 1

Our first approach involved the preparation of boronate **1** via direct hydroboration of propiolaldehyde diethyl acetal using pinacolborane[15] followed by acid catalyzed deprotection of the acetal (Scheme 2.3). One attractive feature of this proposed synthesis is the fact that no by-product is generated along the way. In principle, this means that no distillation should be required. Although we successfully generated the required pinacolborane, its reaction with the alkyne proved to be rather sluggish.



Scheme 2.3. Attempted synthesis of **1**.

We next envisioned that boronate **1** could be prepared via its boronic acid intermediate **8** (Scheme 2.4). An extensive literature search revealed no reported practical route to this class of compound despite their enormous synthetic potential. The amorphous nature of boronic acids, their amphiphilic character and their instability towards silica gel chromatography make them difficult to both handle and purify.



Scheme 2.4. Proposed general synthetic route to *E*-1-alkenylboronic acids and boronates

2.2.2 Synthesis of boronate 1 via its boronic acid precursor

Over the years, numerous hydroboration reagents have been developed. Among the most common of these are disiamylborane,[16] thexylborane,[16] dicyclohexylborane,[16] 9-BBN,[17] catecholborane,[18] di(isopropylprenyl)borane,[19] dibromoborane,[20] dichloroborane,[21] and diisopinocampheylborane[22] (Figure 2.1). With the exception of the first three, all of these reagents have found application in the transformation of alkynes into

alkenylboronic acids and (or) their derivatives. However, most of these reagents suffer some drawbacks.

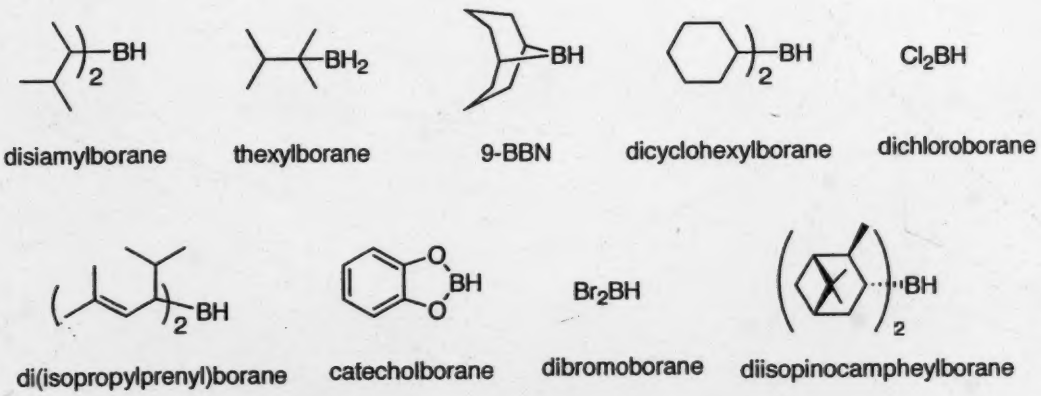


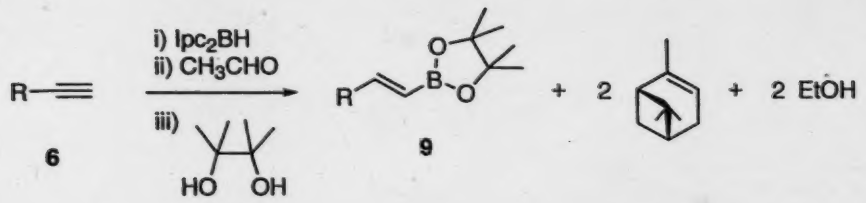
Figure 2.1. Some common hydroboration reagents

For instance, like dicyclohexylborane (*vide supra*), hydroboration using di(isopropylprenyl)borane is followed by oxidation with water, acetone or acetaldehyde. Once again, the alcohol side-product generated in this operation would be very difficult to remove. Perhaps for this reason, only applications to the synthesis of 1-*E*-alkenylboronic esters have been reported so far. Catecholborane[18] constitutes the reagent of choice for the synthesis of (*E*)-1-alkenylboronic acids. However, this reagent does not tolerate acetal or ether functionalities at the propargylic carbon.[14,23] In addition, hydrolysis of the boronate following the catecholboration generates an equimolar amount of acidic catechol, which must be removed by recrystallization. In our hands, this isolation procedure proved difficult and not always reliable. In contrast, no alcohol by-product is generated in the hydroboration using dibromoborane or dichloroborane; however, the lack of chemoselectivity limits their applications.

Diisopinocampheylborane,[22] shown in Figure 2.1, is a mild reagent that has been used extensively in the asymmetric hydroboration of alkenes. To date, however, it has not received as much attention in the hydroboration of alkynes.[23,24] An attractive feature of this reagent is that no diol side-product is generated in the work-up of the reaction. This aspect potentially makes the isolation and purification of the alkenylboronic acid product much easier than for the other hydroboration reagents previously mentioned. In our case, a system using diisopinocampheylborane was successfully applied to the synthesis of various functionalized alkenylboronic acids. This work will now be discussed.

2.2.3 Synthesis of free alkenylboronic acids using diisopinocampheylborane

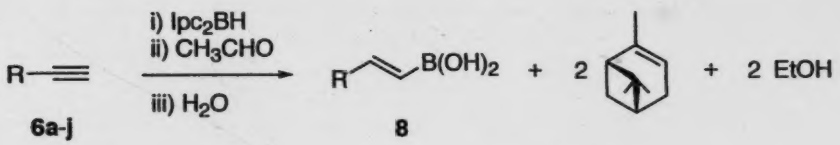
The mildness and selectivity of alkene hydroborations associated with diisopinocampheylborane prompted us to explore this method for alkyne hydroboration. Typically, an alkyne precursor **6** undergoes hydroboration, and is then subjected to oxidative dealkylation using acetaldehyde to afford a diethylboronate along with two equivalents of pinene, a relatively volatile non-polar side product (Scheme 2.5). Additionally, unlike the reagents mentioned above, the hydrolysis of the boronic ester in this case would produce ethanol, which can also be removed by simple aqueous work-up. Surprisingly, no reports on the preparation of boronic acids using this strategy have appeared in the literature.[25] In collaboration with Michel Gravel, we then set out to explore the feasibility of this hydrolysis approach as a convenient route to boronic acids.

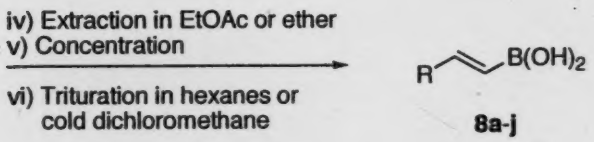


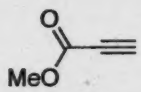
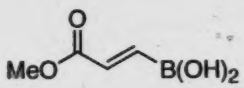
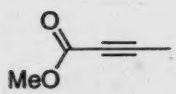
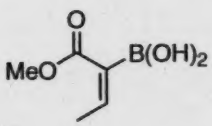
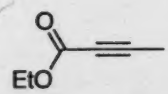
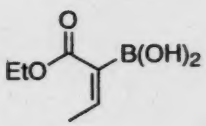
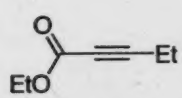
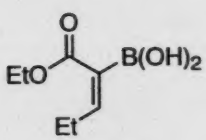
Scheme 2.5. Applications of diisopinocampheylborane to the synthesis of boronic esters.

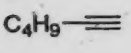
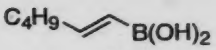
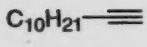
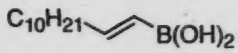
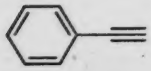
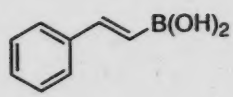
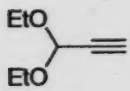
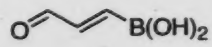
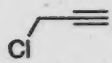
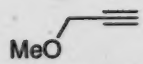
Various alkynes **6a-j** were subjected to a standard protocol consisting of hydroboration with diisopinocampheylborane, followed by treatment with acetaldehyde, hydrolysis, and extraction of the reaction mixture using ether or ethyl acetate (Table 2.1). As anticipated, we found that the poorly soluble boronic acids could be easily purified by concentration of the organic phase, followed by trituration of the precipitate with hexane or cold dichloromethane. The latter operation eliminated all residual pinene and afforded the corresponding free boronic acids (**8a-j**) in good to excellent yield and in high purity.

Table 2.1. Synthesis and purification of free (*E*)-1-alkenylboronic acids





entry	Alkyne	product[a]	yield (%)[b]
1[c]	 **6a**	 **8a**	70
2[c]	 **6b**	 **8b**	49
3[c]	 **6c**	 **8c**	64
4[c]	 **6d**	 **8d**	62

5[c]	 **6e**	 **8e**	51
6[c]	 **6f**	 **8f**	61
7	 **6g**	 **8g**	80
8	 **6h**	 **8h**	80
9	 **6i**	**8i**	51
10	 **6j**	**8j**	84

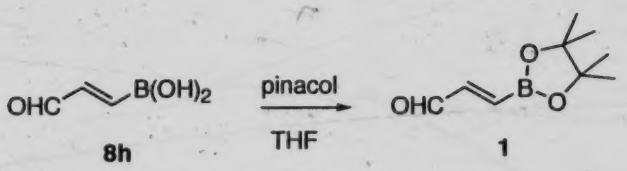
[a] Products isolated as a mixture of the free boronic acid and the corresponding boronic anhydride. [b] Yield of isolated, analytically pure product. [c] Result obtained by Michel Gravel.

All these boronic acids were obtained as air-stable white solids, and ^{1}H NMR analysis indicated the presence of a single regioisomer. Interestingly, we observed a complete reversal of regioselectivity between entries 1 and 2, indicating a competition between steric and electronic factors in the hydroboration of these alkynoates. This simple isolation procedure also allowed the preparation of functionalized alkenylboronic

acids such as **8h-8j**. It is noteworthy that 3-borono-acrolein (**8h**) was obtained directly as the free aldehyde, following *in situ* hydrolysis of the diethyl acetal.

2.2.4 Synthesis of alkenylboronic esters

This approach greatly facilitates access to various alkenylboronates following protection of the boronic acid moiety (Equation 2.1). For example, the important synthetic intermediate, boronoacrolein **1**, is easily obtained in pure form by condensation of boronic acid **8h** with pinacol and simple evaporation of the solvent. The desired boronate was obtained in pure form and in quantitative yield without any distillation. Boronate **10** was prepared in a similar fashion. The addition of ethanolamine to a THF solution of **8h** resulted mainly in the formation of a white solid precipitate, which is characteristic of this type of reaction. Unfortunately, the product was only partially soluble in aprotic solvents. For this reason, further derivatization of this compound could not be achieved. Also, the corresponding catechol boronate **11** could not be synthesized using this strategy (Figure 2.2).



(2.1)

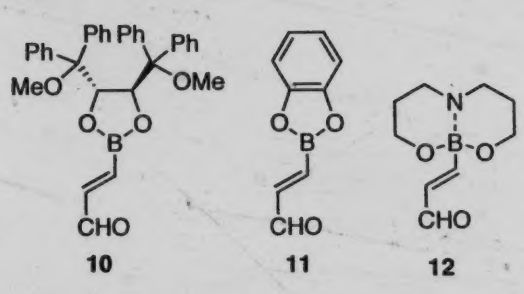


Figure 2.2. Examples of akenylboronates prepared

2.3 Conclusion

In conclusion, we have developed a practical isolation procedure that facilitates the preparation of *E*-alkenylboronic acids, with high purity. This new protocol gives direct access to various functionalized *E*-1-alkenylboronic acids through an efficient work-up procedure featuring an extraction in ether followed by a high-yielding trituration in hexanes or cold dichloromethane. This method can also be applied to alkenylboronic acids that are not readily accessible by other routes

2.4 Experimental

Unless otherwise noted, all operations were carried out in oven or flame-dried glassware under a dry, oxygen-free nitrogen or argon atmosphere. Dichloromethane, methanol, acetonitrile, and toluene were freshly distilled from calcium hydride prior to use. Anhydrous THF was distilled from sodium/benzophenone in a recycling still. Reagents and starting materials were obtained from commercial suppliers and used without further purification unless otherwise noted. Pinacol was recrystallized from benzene and dried under vacuum. Chromatography refers to flash chromatography on silica gel (230-400 mesh). Thin-layer chromatography (TLC) was performed on Merck

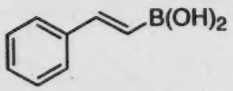
precoated Silica Gel $60F_{254}$. Visualization was obtained with UV light or by exposure to either 5% phosphomolybdic acid in ethanol or aqueous 1% $KMnO_4$ solution. Proton nuclear magnetic resonance (^1H NMR) and carbon NMR (^{13}C or apt) spectra were recorded on Bruker AM 300, Variant INOVA-300, INOVA-400, or INOVA-500 MHz machines as noted individually. The residual solvent protons (^1H) or solvent carbons (^{13}C) were used as internal standard. The NMR data are presented as follows: chemical shifts are expressed in parts per million (ppm) and recorded relative to tetramethylsilane (multiplicity, coupling constant, integration). Coupling constants are expressed as *J* values in Hertz units (Hz) and are accurate to +/- 0.4-0.6 Hz. The following abbreviations are used: app = apparent, s = singlet, d = doublet, dd = doublet of doublet, ddd = doublet of doublet of doublet, t = triplet, dt = doublet of triplet, p = pentet, m = multiplet and br = broad, dm = doublet of multiplet. Infrared spectra were recorded on a Nicolet Magna-IR™ 750 by the University of Alberta spectral services. Frequencies are expressed in cm^{-1}. Elemental analyses (C, H, N) were performed by the Micro-Analytical Lab of the University of Alberta services. High resolution electrospray mass spectra (HRMS) were were recorded by the University of Alberta Mass Spectrometry Laboratory Services using either electron impact (EI) or electrospray ionization techniques. Significant protonated molecular ions $[M+H]^+$ as well as peaks corresponding to sodiated molecular ions $[M+Na]^+$ were present in most of the spectra because of trace amounts of sodium salts in the samples. Melting points were determined using a Gallenkamp apparatus and are uncorrected. For boronic acids, elemental analyses were not obtained as it is well known that these compounds, obtained from mixed aqueous organic solutions, exist as variable mixtures of free acid and the corresponding boroxines.[26] Compounds **8a**-

8f were prepared by Michel Gravel;[27] therefore, the characterization data of these compounds are not listed in this thesis. Boronate **12** could not be characterized due to its low solubility in aprotic solvents. Carbons that are directly attached to boron are oftentimes not observed on APT spectra. In addition, some labile protons (NH and OH) are not always observed in NMR spectra.

2.4.1 General procedure for the preparation of *E*-1-alkenylboronic acids

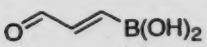
(*R*)-(+)-α-Pinene (91% ee, 3.18 ml, 20 mmol) was slowly added to a solution of borane-dimethyl sulfide complex (1.00 mL, 10 mmol) in THF (2 mL) at 0° C. The solution was warmed up to room temperature and stirred for two hours. The resulting thick white suspension was cooled to -40° C and the alkyne (10 mmol) was added dropwise. The mixture was allowed to warm up to room temperature and stirred for 2 to 24 hours. The resulting solution was cooled to 0° C and freshly distilled acetaldehyde (8 mL) was slowly added. The mixture was then refluxed for 16 hours at 45° C, then water (15 mL) was added at 0° C. The biphasic mixture was vigorously stirred for 3 hours and the top organic layer was decanted. The aqueous layer was extracted 3 times with 30 mL of ether and/or with ethyl acetate (2 × 10 mL), and then the organic layers were combined and concentrated on a rotary evaporator. The resulting suspension was triturated in cold hexanes then filtered, and rinsed with cold hexane or cold dichloromethane to yield the boronic acid **8** as a white solid. A second crop could be obtained by concentration of the filtrate and trituration in cold hexane. If the product was still coloured, it could be washed with cold dichloromethane.

(*E*)-Styrylboronic acid (8g)[28,29]



White solid (0.77 g, 80%); mp 145-148° C; ^{1}H-NMR (400MHz, CD_3OD + 5% D_2O) δ 7.50-7.45 (m, 2H), 7.34-7.22 (m, 4H), 6.15 (d, *J* = 13.5 Hz, 1H); ^{13}C (100 MHz, CD_3OD + 5% D_2O) δ 148.3, 148.2, 139.1, 129.6, 127.9; FTIR (film cast) 3020, 1615, 1574, 1493, 1438 cm^{-1}; HRMS (EI, *m/z*) calcd for $C_8H_9O_2B$ 148.0696 found 148.0699.

(*E*)-3-Boronoacrolein (8h).



White solid (5.3 g, 80%); mp 128-131 °C; ^{1}H NMR (400 MHz, CD_3OD + 5% D_2O) δ 9.52 (d, *J* = 7.5 Hz, 1H), 6.80 (d, *J* = 18.0 Hz, 1H), 6.64 (dd, *J* = 18.0, 7.7 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD + 5% D_2O) δ 197.6, 145.6, 105.1; FTIR (film cast) 3175, 2850, 1673 cm^{-1}; HRMS (EI, *m/z*) calcd for $C_3H_5O_3B$ 100.0332 found 100.0334.

(*E*)-3-Chloro-prop-1-enylboronic acid (8i).

White solid (04 g, 51%), mp 110-112°C; ^{1}H NMR (400 MHz, CD_3OD + 5% D_2O) δ 6.50 (dt, *J* = 6.1, 17.6 Hz, 1H), 5.69 (d, *J* = 17.4 Hz, 1H), 4.11 (dd, *J* = 1.3, 6.1 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD + 5% D_2O) δ 145.4, 126.9, 47.0; FTIR (film cast) 3213, 1640 cm^{-1}; HRMS (EI, *m/z*) calcd for $C_3H_6O_2BCl$ 120.0155 found 120.0147.

(*E*)-3-Methoxy-prop-1-enylboronic acid (8j).

White solid (0.61 g, 845%); mp 124-127 °C; ^{1}H NMR (400 MHz, CD_3OD + 5% D_2O) δ 6.54-6.40 (m, 1H), 5.68-5.56 (m, 1H), 3.98-3.96 (m, 2H), 3.33 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD + 5% D_2O) δ 146.9, 75.3, 58.4; FTIR (film cast) 3184, 2998 cm^{-1}; HRMS (EI, *m/z*) calcd for $C_{12}H_{21}O_6B_3$ 294.1617 found 294.1628 (only boroxine detected).

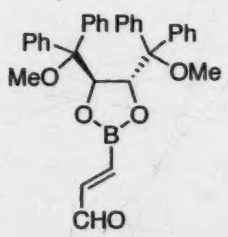
3-Boronoacrolein pinacolate (1).[14]

The 3-borono-acrolein (**8h**) (1.00 g, 10.0 mmol) was dissolved in THF (25 mL) at room temperature, and dry pinacol (recrystallized from dichloromethane) (1.12 g, 10.0 mmol) was added. The solution was stirred for 30 minutes then the solvent was evaporated under reduced pressure at 45° C to afford a colorless oil in quantitative yield. Addition of THF followed by concentration may be necessary to complete the condensation by azeotropic removal of the water. Analytically pure boronate **1** was obtained by Kugelrohr distillation (0.1 torr, 90° C).

Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (dd, *J* = 1.2, 8.7 Hz, 1H), 6.76 (dd, *J* = 8.6, 18.1 Hz, 1H), 6.62 (dd, *J* = 1.2, 18.1 Hz, 1H), 1.26 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.64, 146.8, 142.22, 84.4, 24.9;

(4R, 5R)-2-(4-Oxo-*E*-prop-2-enyl)-4,5-bis[methoxy(diphenyl)methyl]-1,3,2-dioxaborolane (10).

This compound was prepared as described above for compound **1**. In this case, a white solid was obtained. The solid was dissolved in THF, and the solvent was evaporated. This operation was repeated two more times to make sure that the reaction was completed. Analytically pure sample was obtained following flash chromatography using 10% ethyl acetate in hexane.



White solid (quantitative), ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (d, J = 7.7Hz, 1H), 7.46-7.21 (m, 20H), 6.35 (dd, J = 7.6, 18.1 Hz, 1H), 6.20 (d, J = 18.1 Hz, 1H), 5.42 (s, 2H), 3.0 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.9, 146.8, 140.8, 129.7, 128.4, 128.3, 128.0, 127.8, 127.6, 127.4, 83.3, 78.3, 51,9; FTIR (film cast) 3058, 3032, 2939, 2832, 1696, 1620, 1494, 1381, 1340, 1269, 1240 cm^{-1}; HRMS (EI, m/z) calcd for $C_{33}H_{31}O_5BNa$ 541.2157 found 541.2163; elemental analysis calcd (%) for $C_{33}H_{31}O_5B$ (518): C 76.43, H 5.98; found: C 76.37, H 6.06; $[\alpha]_D^{23}$ = -155 (c = 0.35 in $CHCl_3$).

2.5 References and notes

(1) Brown, H. C.; Subba Rao, B. C. *J. Am. Chem. Soc.* **1956**, *78*, 5694–5695.

(2) Miyaura, N.; Suzuki, A. *J. Chem. Soc. Chem. Commun.* **1979**, 866–867.

(3) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147-168.

(4) Miyaura, N. *J. Organomet. Chem.* **2002**, *653*, 54–57.

(5) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798-11799.

(6) Sakai, M.; Ueda, M.; Miyaura, N. *Angew. Chem. Int. Ed.* **1998**, *37*, 3279-3281.

(7) Ueda, M.; Miyaura, N. *J. Org. Chem.* **2000**, *66*, 4450-4452.

(8) Sakuma, S.; Miyaura, N. *J. Org. Chem.* **2001**, *66*, 8944-8946 and references therein.

(9) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829-2844.

(10) For early examples, see: (a) Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933-2936. (b) Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett.* **1998**, *39*, 2937-2940. (c) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941-2944. (d) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Averill, K. M.; Chan, D. M. T.; Combs, A. *Synlett* **2000**, 674-676.

(11) Herradura, P. S.; Pendola, K. A.; Guy, R. K. *Org. Lett.* **2000**, *2*, 2019-2022.

(12) Vaultier, M.; Truchet, F.; Carboni, B.; Hoffmann, R.W.; Denne, I. *Tetrahedron Lett.* **1987**, *28*, 4169-4172.

(13) (a) Tailor, J.; Hall, D.G. *Org. Lett.* **2000**, *2*, 3715-3718. (b) Touré, B. B.; Hoveyda, H. R.; Tailor, J.; Ulaczyk-Lesanko, A.; Hall, D .G. *Chem. Eur. J.* **2003**, *9*, 466-474.

(14) Kamabuchi, A.; Moriya, T.; Miyaura N.; Suzuki, A. *Synth. Commun.* **1993**, *23*, 2851-2850.

(15) Tucker C. E.; Davidson, J.; Knochel P. *J. Org. Chem.* **1992**, 3482-3485.

(16) Brown, H. C. *Boranes in Organic Chemistry*; Cornell University Press: Ithaca, New York, 1972; 227-446.

(17) Soderquist, J. A.; Negron, A. *Org. Synth.* **1992**, *70*, 169-176.

(18) Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1971**, *93*, 1816-1818.

(19) Kalinin, A. V.; Scherer, S.; Snieckus, V. *Angew. Chem. Int. Ed.* **2003**, *42*, 3399-3404.

(20) Brown, H. C.; Campbell, J. B. *J. Org. Chem.* **1980**, *45*, 389-395.

(21) Josyula, K. V. B.; Gao, P.; Hewitt, C. *Tetrahedron Lett.* **2003**, *44*, 7789-7792.

(22) Brown, H. C.; Singaram, B. *J. Org. Chem.* **1984**, *49*, 945-947.

(23) Hoffman, R. W.; Dresely, S. *Synthesis* **1988**, 103-106.

(24) For example, see: Mortier, J.; Vaultier, M.; Plunian, B.; Toupet, L. *Heterocycles* **1999**, *50*, 703-711.

(25) During the course of our work, a similar route to boronic acid **8h** was disclosed although no detail experimental procedure was published: Deligny, M.; Carreaux, F.; Carboni, B.; Toupet, L.; Dujardin, D. *Chem. Commun.* **2003**, 276-277.

(26) Santucci, L.; Gilman, H. *J. Am. Chem. Soc.* **1958**, *80*, 193-196.

(27) Gravel M. *Ph.D. Thesis*, University of Alberta, Edmonton, Alberta **2004**.

(28) Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1972**, *94*, 4370-4371.

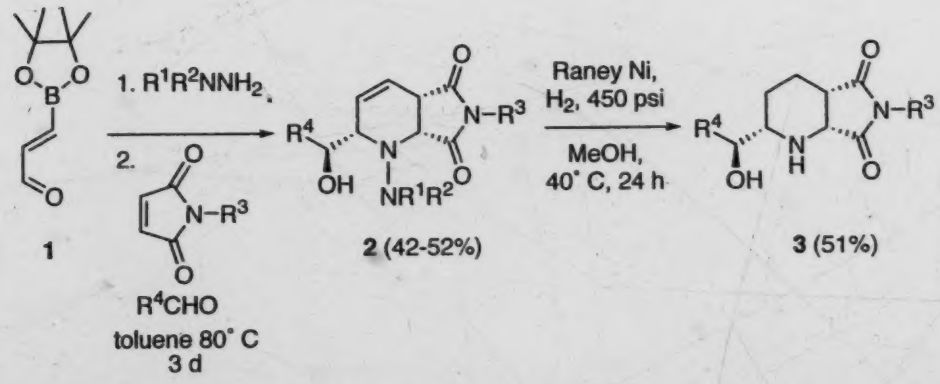
(29) Matteson, D. S.; Jesthi, P. K. *J. Organomet. Chem.* **1976**, *110*, 25-37.

Chapter 3

A Three-Component Tandem Aza[4+2]/Allylboration Approach to Polysubstituted α-Hydroxyalkyl Piperidines

3.1 Introduction

Now that we have secured an efficient route to 3-boronoacrolein pinacolate **1** (Chapter 2), we next sought to gain more insight into the scope of the three-component aza[4+2]cycloaddition/allylboration reaction reported earlier by our laboratory.[1] At the outset, the syntheses of the dienes and of the multicomponent reaction (MCR) adducts **2** were low yielding. In addition, the reaction proceeded only slowly under thermal conditions due to the low reactivity of the diene component (Scheme 3.1).



Scheme 3.1. Three-component approach to α-hydroxyalkyl piperidine by Hall and Tailor.

It was hoped that our studies would unveil new variants of the reaction that in turn would facilitate the total synthesis of some of the bioactive natural products depicted in Figure 3.1.

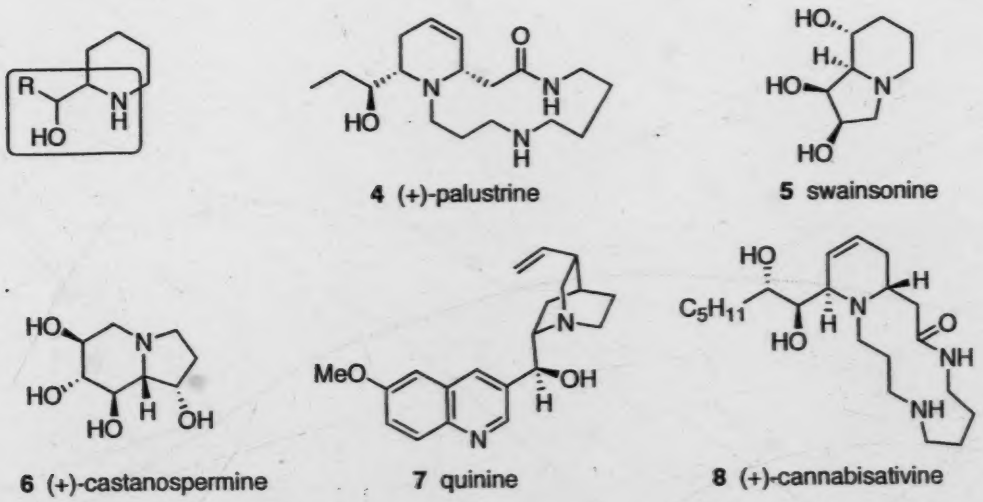


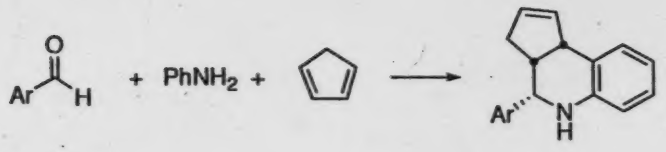
Figure 3.1. Selected examples of natural products containing α-hydroxyalkyl piperidine units.

Our interest in this class of compounds arose from the presence of a piperidine ring flanked by a stereodefined α-hydroxyalkyl side chain. This structural template has not, so far, received much attention for diversity-oriented synthesis (DOS) applications despite the promising biological activities displayed by some alkaloids that belong to this subfamily (Figure 3.1). For instance, (+)-palustrine (**4**) is known to cause weight loss subsequent to loss of appetite,[2] whereas swainsonine (**5**) and castanospermine (**6**)[3] are potent glycosidase inhibitors[4]. Glycosidase inhibitors have many potential therapeutic applications. They are currently marketed for the treatment of type 2 diabetes,[5] and

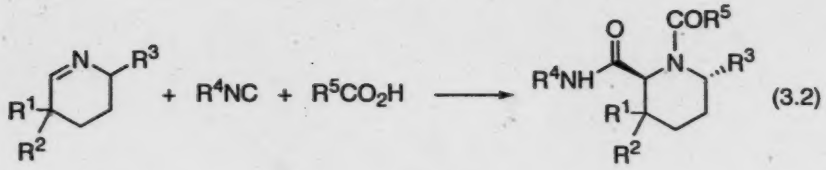
influenza virus infections[6]. In addition, they could be potentially used for the treatment of HIV infections, hepatitis and cancer.[3]

Although they are endowed with a variety of biological activities, the alkaloids shown in Figure 1 only share in common the presence of an α-hydroxyalkyl piperidine moiety. An understanding of the biological activity, if any, of this simple motif could then shed light on the mode of action of these complex natural products and potentially lead to the development of simple analogues with improved biological profile.

The challenge underlying the stereocontrolled synthesis of α-hydroxyalkyl piperidine moiety will be discussed in much more detail in Chapter 4. Though at this point, it is worth noting that none of the existing approaches to this structural unit relied on a MCR strategy. Indeed, prior to work done in this research group, there were no MCRs for the synthesis of α-hydroxyalkyl piperidine motif despite the obvious synthetic appeal of these processes.[7] Moreover, despite the intense synthetic activities,[8] there are still very few MCRs to construct simple piperidine derivatives. In addition to the ones discussed in Chapter I, these specific cases include the Grieco three-component reaction (Equation 3.1)[9] along with a limited number of Ugi-type condensations (Equation 3.2)[10]. However, neither of these reactions easily accommodate the formation of an α-hydroxyalkyl group. Similarly, although both the Petasis borono-Mannich reaction (Equation 3.3)[11] and modified Passerini condensations (Equation 3.4)[12] are powerful MCRs, giving access to acyclic α-aminoalcohol units, these processes have not been applied to the construction of α-hydroxyalkyl piperidines.[13]



(3.1)



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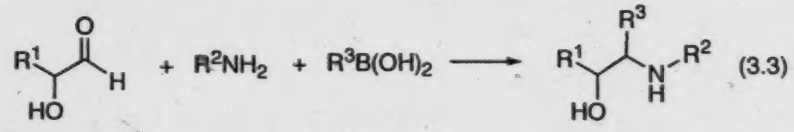
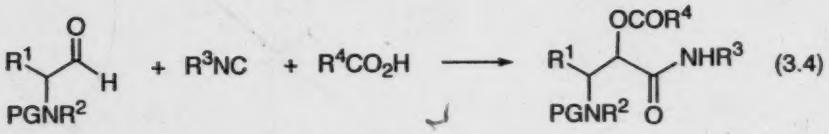


(3.3)

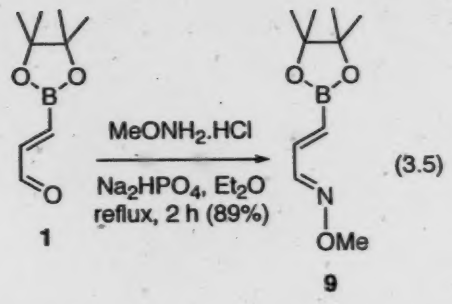


(3.4)

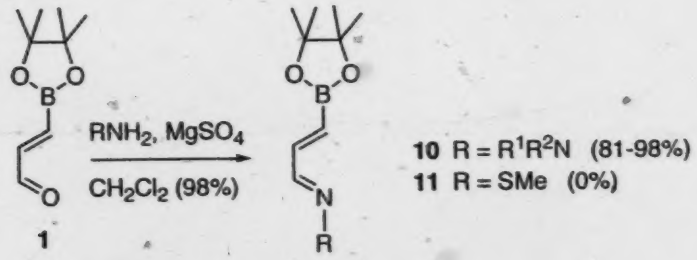
3.2 Results and Discussion

3.2.1 Synthesis of the dienes

We have discussed in the previous chapter our synthetic approach to functionalized *E*-1-alkenylboronic acids and their derivatives. We have also demonstrated that these boronic acids could be easily converted to the appropriate boronic ester such as 3-boronoacrolein **1**. Hall and Taylor reported a condensation protocol of the latter compound with various hydrazines.[1] The reaction was performed in refluxing ether buffered with an aqueous phosphate solution. This procedure proved to be the best method for the preparation of *N*-alkoxy diene **9** (Equation 3.5).

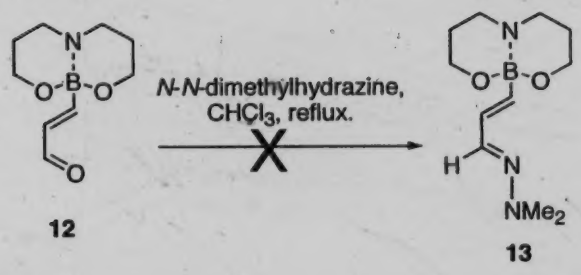


Hydrazonodienes **10** were also prepared using the above procedure,[1] but the reaction was low yielding probably due to the fact that these dienes are sensitive to moisture. We then sought to carry out this transformation under anhydrous conditions. To this end, magnesium sulfate was employed as dehydrating agent. Boronohydrazonodienes **10** were obtained in almost quantitative yield using this improved procedure (Scheme 3.2) and (Table 3.1). However, our attempt to prepare compound **11** only met with failure.



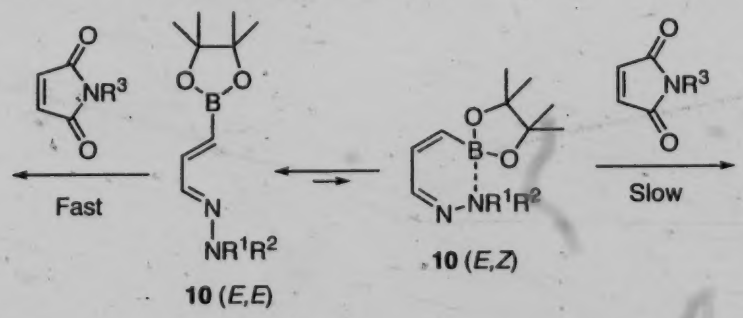
Scheme 3.2. Synthesis of hydrazonodienes.

Likewise, aldehyde **12** failed to deliver the desired product **13** even under high dilution conditions (Equation 3.6).



12 13 (3.6)

Interestingly, we have noticed that some of the 4-borono-hydrazonodienes **10** tend to undergo a thermal *trans-cis* isomerization around the C3-C4 bond (Scheme 3.3). This phenomenon was further studied using dialkylhydrazonodiene **10a** as model compound. The latter is typically obtained from aldehyde **1** as a mixture favoring the *E,E*-isomer in a ratio varying between 2:1 to 5:1. The occurrence of the minor *E,Z* isomer may be explained by formation of a cyclic structure (5 or 6-membered) with favorable N-B coordination. The identity of these isomers was deduced from the coupling constants between all the olefinic hydrogens. The two isomers are not separable by chromatography. In addition, the yield of the reaction, in some cases, is higher than the observed (*E,E*) over *E,Z* ratio of the two isomers. The latter result suggests that the isomerization of the dienes may be a dynamic interconversion process. Likewise, many other dienes were observed as a mixture of many isomers, most of which could not be completely characterized. Fortunately, this phenomenon was inconsequent for the optimization of the three-component reaction.

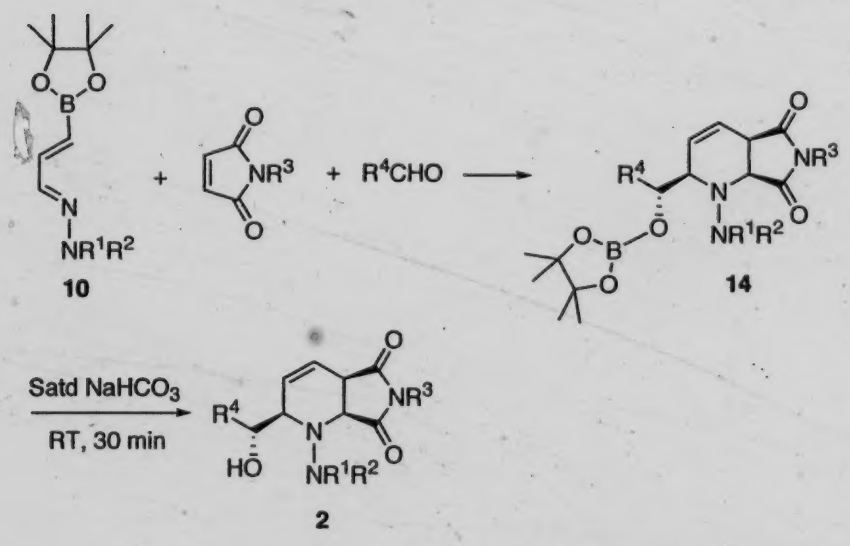


Scheme 3.3. Diene isomerization phenomenon.

3.2.2 Tandem aza [4+2]/allylboration reaction

With this practical diene preparation procedure in hand, several combinations of substrates were explored in order to assess the generality of the tandem aza[4+2]cycloaddtion/allylboration MCR process and its potential towards applications in diversity-oriented synthesis (Table 3.1). For this purpose, maleimides were chosen as model dienophiles, and a variety of commercially available aldehydes and hydrazines were used as variable components.

Table 3.1. Tandem aza[4+2]cycloaddition/allylboration route to α-hydroxyalkyl piperidine derivatives.[a]



Entry	Diene	R^1	R^2	Dienophile R^3	Aldehyde R^4	Ratio	Product	Yield [%][b]
1	**10a**	Me	Me	Ph	Ph	1:2:1	**2a**	47
2	**10a**	Me	Me	Ph	Ph	3:1:1	**2a**	75
3[c]	**10a**	Me	Me	Me	Ph	1:2:1	**2b**	50
4[c]	**10a**	Me	Me	Ph	4-$NO_2C_6H_4$	1:2:1	**2c**	48
5[c]	**10a**	Me	Me	Ph	4-$MeOC_6H_4$	1:2:1	**2d**	52
6	**10a**	Me	Me	Me	2-MeC_6H_4	2:1:1	**2e**	50
7[c]	**10a**	Me	Me	Ph	*i*-$PrCH_2$	1:2:1	**2f**	50
8	**10a**	Me	Me	Me	C_6H_{11}	2:1:1	**2g**	39
9	**10a**	Me	Me	Me	2,4,6-Me-C_6H_2	1:2:1	**2h**	-
10	**10b**	H	Ph	Ph	Ph	1:2:1	**2i**	76
11	**10c**	H	4-$CF_3C_6H_4$	Me	Ph	1:2:1	**2j**	77
12	**10d**	H	4-$MeOC_6H_4$	Me	Ph	1:2:1	**2k**	55
13	**10e**	Me	Ph	Ph	Ph	1:2:1	**2l**	65
14	**10e**	Me	Ph	Ph	2-$MeOC_6H_4$	2:1:1	**2m**	68
15[c]	**10f**	H	Ac	Ph	Ph	1:2:1	**2n**	42

[a]All reactions were carried out by heating a mixture of diene:dienophile:aldehyde in ratio indicated above in anhydrous toluene [~0.2M] at 80 °C for 72 hours.
[b]Unoptimized yields of products isolated after flash chromatography purification.
[c]Compounds were prepared by Jyoti Tailor.

The bicyclic adducts **2** were obtained following a basic aqueous work-up and flash chromatography purification. In all cases, only one diastereomer was observed via ^{1}H-NMR analysis of the crude reaction products. In general, the use of diene **10a** as a limiting reagent provided modest yields of product that were nonetheless comparable with those reported for the analogous reactions of 1,3-dienylboronates.[14] Alternatively, when an excess of diene **10a** was employed (3:1:1 diene/dienophile/aldehyde ratio) the yield of bicyclic adduct **2a** was raised significantly from 47% to 75% (entries 1&2).[1] We suspect that heterodienes such as **2a** made from non-aromatic hydrazines are prone to thermal decomposition, thereby causing a reduction in the yield of desired product when they are used as a limiting component. Unsurprisingly, the maleimide substituent (R^3) can be varied without affecting product yield (i.e., **2a** vs **2b**, entries 1&3). Most importantly, the isolation of compounds **2c**-**2g** (entries 4-8) shows that a wide variety of aldehydes can be employed, including aliphatic ones as well as both electron-rich and electron-poor aromatic derivatives. However, the use of very hindered aldehydes such as *ortho*-disubstituted ones (e.g., entry 9), failed to provide the desired products. Although the prospect for using diverse hydrazone substituents is irrelevant to the synthesis of free piperidines (they are accessible through reductive cleavage of the hydrazine), it is undoubtedly appealing towards combinatorial chemistry applications. Hydrazines and hydrazides are indeed present as pharmacophores in several pharmaceuticals.[15] By including both hydrazone substituents in **10** (R^1, R^2), the three components in this multicomponent reaction deliver four elements of diversity into the compact bicyclic scaffold of products **2**. As shown with the isolation of products **2i**-**2m** (entries 10-14), heterodienes **10b**-**10e** made from both mono- and disubstituted arylhydrazines are also

highly effective substrates. We observed that these heterodienes tend to show superior thermal stability as compared to **10a** and consequently gave higher yields of products even when used as the limiting reagents.

3.2.3 Other dienophiles and dienes

Other dienophiles were tested for their applicability in this reaction. In all cases, the tandem reaction was either not proceeding, or gave products that apparently decomposed and/or gave unidentified side products at elevated temperatures (Figure 3.2).

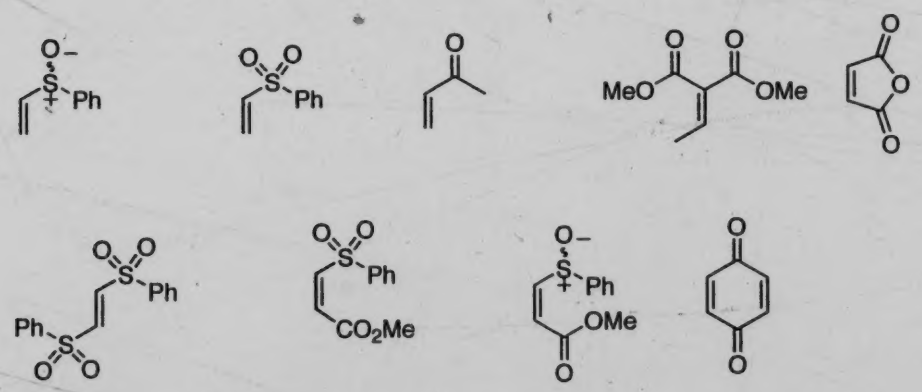


Figure 3.2. Other dienophiles tested in the tandem aza[4+2]/allylboration.

Similarly, diene **9** proved unreactive despite significant effort. Nonetheless, by offering such a wide scope of substituents for both the aldehyde and hydrazine components, this MCR offers significant potential towards diversity-oriented syntheses of polysubstituted piperidine derivatives.

3.2.4 Mechanistic proposal for the tandem [4+2]/allylboration.

Mechanistically, the [4+2] cycloaddition of heterodienes **10** with maleimides is expected to proceed with complete *endo* selectivity to give the allylboronate intermediate shown in Figure 3.3. From this, the stereochemical outcome of the allylation step can be explained via the usual cyclic chair-like allylboration transition state involving *anti* coordination of the aldehyde to the boronyl group oriented axially on the *endo* face of the piperidine ring. It is noteworthy that this system constitutes a rare example of allylboration reaction involving γ-amino-substituted allylboryl reagents.[16,17] Moreover, the stereochemistry of the resulting 1,2-aminoalcohol unit is the same as that of several alkaloids including swainsonine and methyl palustramate (Figure 3.1), thus confirming the potential of this strategy in natural product synthesis. This transition state was proposed in light of the observed product stereochemistry, which was established by X-ray diffraction.[1,18] The stereochemical outcome also mirrors that of the carbocyclic series.[19]

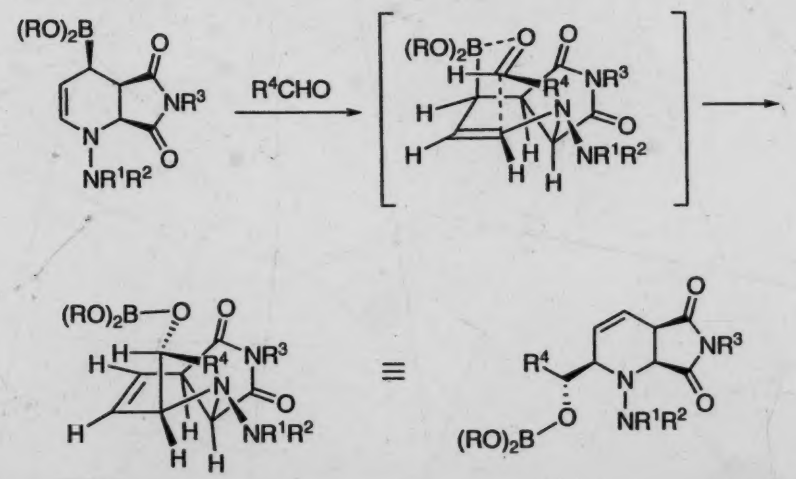
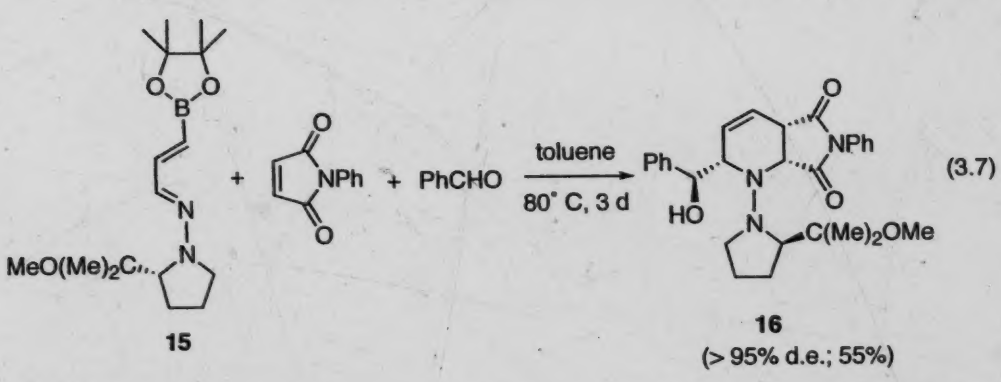


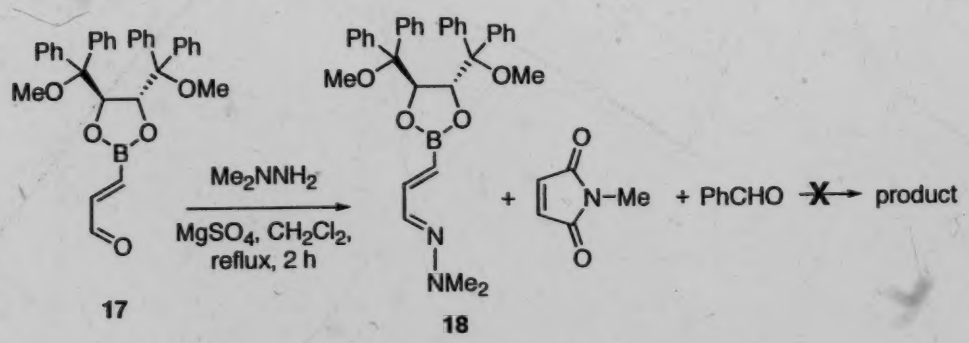
Figure 3.3. Proposed transition state to rationalize the stereochemistry resulting from the allylboration step.

3.2.5 Asymmetric synthesis of α-hydroxyalkyl piperidine derivatives

The control of the absolute stereochemistry in this tandem hetero[4+2]/allylboration process using the Ender's auxiliary[20] was initially explored by Jyoti Taylor and was further investigated during the course of this work. Diene **15**, obtained from the reaction of Ender's auxiliary[20] with our boronate **1**, was reacted with *N*-phenylmaleimide, and benzaldehyde to provide bicycle **16** in a remarkable >95% d.e (Equation 3.7).[1,21,22] Thus, in addition to the high level of diastereoselectivity observed in this tandem hetero[4+2]/allylboration process, it is also possible to control the absolute stereochemistry of the bicyclic structure using a chiral auxiliary approach.



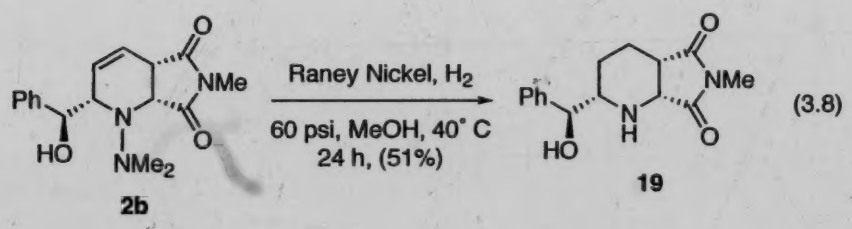
We also briefly explored the possibility of a remote stereoinduction. Towards this goal, the chiral boronate **17** (prepared in the previous chapter) was first condensed with *N,N*-dimethylhydrazine and the resulting diene **18** was subjected to our three-component reaction conditions. Unfortunately, no desired product was isolated under the normal reaction conditions and increasing the reaction temperature only resulted in decomposition (Scheme 3.4). Obviously the steric created by the huge boronate auxialliary hinders the approach of the dienophile.



Scheme 3.4. Synthesis and evaluation of chiral boronodiene **17**.

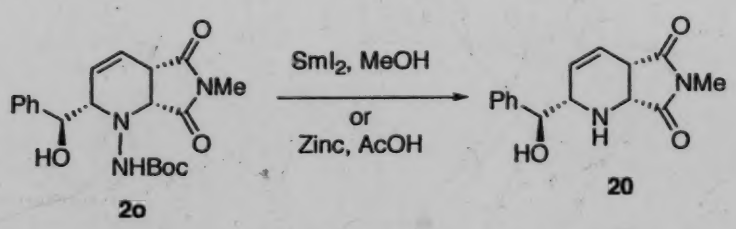
3.2.6 Synthesis of free piperidines

The application of this reaction strategy to the synthesis of natural products rests upon the successful cleavage of the hydrazine moiety to reveal the amine functionality. This task was accomplished using Raneyl Nickel under high pressure and heating conditions as reported Hall and Tailor.[1] The desired amine was obtained in moderate yield after purification, albeit the double bond is also hydrogenated in this process (Equation 3.8).



(3.8)

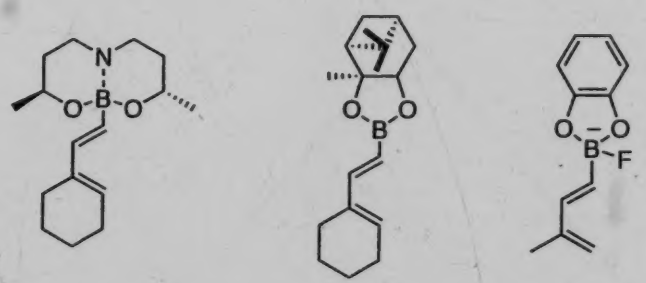
As an attempt to preserve the integrity of the double bond, bicyclic adduct **2o** bearing a carbamate activated hydrazine was treated with either SmI_2[20] or activated zinc. However, these efforts met with limited success. The desired product **20** was only obtained as a minor component of a mixture of products (Equation 3.9).



(3.9)

3.2.7 Catalysis of the tandem Diels-Alder/allylboration reaction.

The low reactivity of dienes **10** has so far precluded the use of monoactivated dienophiles. The Diels-Alder reaction of these dienophiles would deliver products lacking the C3-substituent essential for the synthesis of targets **4** and **8**. Based on literature precedents, we envisioned that the increase of electron density around the boron center or the use of transition metal catalysts could increase the reactivity of dienes of type **10**, thereby broadening the scope of the reaction. Indeed, Wang has documented a significant increase of reactivity for diene **21** over **22**. The former was shown to react with maleimide derivatives at room temperature, and was complete within hours, whereas the latter required days at elevated temperatures.[23] Also, the addition of cesium fluoride to the Diels-Alder cycloaddition involving diene **23** has been shown to accelerate the course of the reaction (Figure 3.4).[24] It is more likely that the increased in the reactivity of these dienes is due to the deconjugation of the HOMO of the diene and the empty orbital of the boron rather than a true electron donation from the tetrahedral borate to the diene.



21 **22** **23**

Figure 3.4. Example of tetracoordinate boronodienes.

Unfortunately, we could not access the corresponding dienes that would have allowed us to take advantage of these opportunities. In addition, no beneficial effect was observed when cesium fluoride was added to a reaction mixture containing dienes of type **10**. Perhaps the steric bulk of the pinacol group hinders the approach of the fluoride. In addition, pinacolboronate are significantly less Lewis acidic than catechol their counterparts.

Likewise, the addition of Lewis-Acids such as $MgCl_2$, $ZnCl_2$, $Yb(OTf)_3$, $Sc(OTf)_3$ to a reaction mixture, under the conditions outlined in table 2.1, resulted mainly in the rapid decomposition of the diene component.

3.3 Conclusion

In conclusion, we have described the scope and limitation of the first three-component tandem aza[4+2]/allylboration reaction, giving access to a wide range of polysubstituted α-hydroxyalkyl piperidines in a highly diastereocontrolled fashion. The required 4-borono-hydrazonodienes were efficiently synthesized from the condensation of 3-boronoacrolein pinacolate **1** with hydrazines under dehydrating conditions. Overall the tandem aza[4+2]/allylboration process was found to be quite general. It tolerates the use of a wide variety of aldehydes and hydrazine precursors with different electronic and steric characteristics. Unfortunately, only maleimide derivatives can be used as dienophile. By allowing a wide substrate scope with respect to aldehyde and hydrazine components, this MCR is particularly well adapted towards applications in diversity-oriented synthesis of polysubstituted piperidine derivatives. The exploration of the biological activity of these compounds is an ongoing effort in our laboratory.

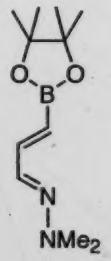
3.4 Experimental

The experimental procedure described in section 2.4 (Chapter 2) also applies here with only few modifications. Compounds **2b-d and 2f and 2n** were prepared by Jyoti Tailor,[25] therefore, the characterization data of these compounds are not listed in this thesis. Compound **2o** was obtained from Agnieszka Ulaczyk-Lesanko. All aldehydes were freshly distilled. Ender's auxialiary was synthesized according to a literature procedure.[20] In some cases, the labile OH and NH protons were not observed in the NMR spectra.

3.4.1 Preparation of the dienes (10)

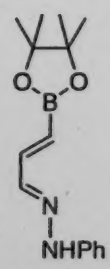
To a solution of aldehyde **1** (1.0 g, 5.5 mmol) in freshly distilled dichloromethane, *N,N*-dimethylhydrazine (0.42 mL, 5.50 mmol) and magnesium sulfate (0.86 g, 7.20 mmol) were added. The resulting mixture was then refluxed for 2 hours. Magnesium sulfate was removed by filtration through a predried fritted funnel. Solvent was evaporated under reduced pressure to afford a yellowish oil as the product (1.2 g, 96%). All dienes **10a-10d** were isolated as a mixture of two inseparable *3E* and *3Z* isomers (see text). NMR assignments are provided only for the major (*E,E*) isomers. These dienes were generally employed immediately in the tandem reactions.

2-[1-dimethylamino-1-aza-(3*E*)-1,3-butadienyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (10a).



Yellow oil (1.2 g, 98%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.15 (dd, J = 8.9, 17.9 Hz, 1H), 6.93 (d, J = 8.9 Hz, 1H), 5.53 (d, J = 17.9 Hz, 1H), 2.95 (s, 6H), 1.22 (s, 12H); ^{13}C (75 MHz, $CDCl_3$, APT): δ = 148.2 (CH), 135.6 (CH), 134.5 (CH), 83.0 (C), 42.4, 24.9; IR ($CHCl_3$ cast): ν = 2977, 2931, 2865, 1548, 1412, 1213, 998, 882, 779 cm^{-1}; MS (ES): m/z 225 $[M+H]^+$; HRMS (ES): m/z calcd for $C_{11}H_{21}BN_2O_2$ 224.1774; found 225.1778 $[M+H]^+$.

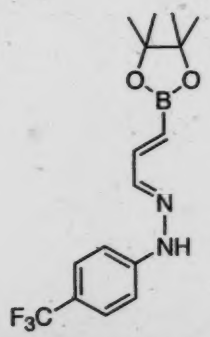
2-[1-phenylamino-1-aza-(3*E*)-1,3-butadienyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (10b)



Yellow oil (0.51 g, 86%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34-7.21 (m, 5H), 6.99 (d, J = 9.0 Hz, 1H), 6.87 (dd, J = 9.0, 18.0 Hz, 1H), 5.68 (d, J = 18.0 Hz, 1H), 1.25 (s, 12H); ^{13}C (75 MHz, $CDCl_3$, APT): δ = 146.4 (CH), 143.9 (C), 139.9 (CH), 129.2 (CH), 120.6 (CH), 120.4 (CH), 112.1 (CH), 82.7 (C), 24.7; IR ($CHCl_3$ cast): ν = 3285, 2977, 2924,

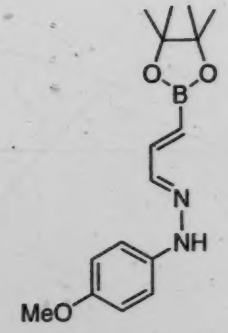
1560, 1446, 1286, 1214, 1070, 899, 648 cm^{-1}; MS (ES): *m/z* 305 $[M+Na]^+$, 273 $[M+H]^+$; HRMS (ES): *m/z* calcd for $C_{15}H_{21}BN_2O_2$ 272.1774; found 273.1769 $[M+H]^+$.

2-[1-(4-trifluoromethyl-phenyl-amino)-1-aza-(3*E*)-1,3-butadienyl]-4,4,5,5-tetramethyl-1,3,2- dioxaborolane (10c)



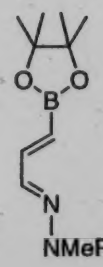
Brown oil (0.68, 83%); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.80 (s, 1H), 7.48 (d, *J* = 6.8 Hz, 2H), 7.42 (d, *J* = 7.5 Hz, 2H), 7.20 (dd, *J* = 7.2, 14.6 Hz, 1H), 7.04 (d, *J* = 6.8, 1H), 5.75 (d, *J* = 14.5 Hz, 1H), 1.23 (s, 12H); ^{13}C (75 MHz, $CDCl_3$): δ = 147.0, 146.6, 141.7, 126.5, 122.7 (q), 112.6, 111.2, 83.6, 25.1; HRMS (EI): *m/z* calcd for $C_{16}H_{20}BF_3N_2O_2$ 340.1570; found 340.1572 $[M]^+$.

2-[1-(4-trimethoxy-phenyl-amino))-1-aza-(3*E*)-1,3-butadienyl]-4,4,5,5-tetramethyl-1,3,2- dioxaborolane (10d)



Yellow oil (0.46 g, 88%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60-7.46 (br s, 1H), 7.36 (d, J = 9.0 Hz, 1H), 7.19 (dd, J = 9.2, 18.3 Hz, 1H), 6.94 (d, J = 9.0 Hz, 2H), 6.80 (d, J = 9.0 Hz, 2H), 5.63 (d, J = 17.7 Hz, 1H), 3.68 (s, 3H), 1.25 (s, 12H); ^{13}C (75 MHz, $CDCl_3$, APT): δ = 154.2 (C), 146.5 (CH), 139.3 (CH), 138.0 (C), 114.8 (CH), 114.6 (CH), 114.1 (CH), 83.4 (C), 55.6 (CH_3), 24.7 (CH_3); HRMS (EI): m/z calcd for $C_{16}H_{23}BN_2O_3$: 302.1800; found 302.1799 $[M]^+$.

2-[1-(*N*-pheny-*N*-methyl)-1-aza-1,3-butadienyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (10e)

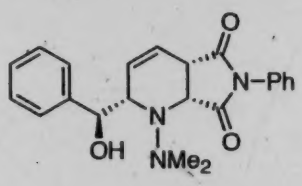


Colorless oil (0.58 g, 81%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25 (m, 5H), 6.98-6.89 (m, 2H), 5.70 (d, J = 15.3 Hz, 1H), 3.34 (s, 3H), 1.26 (s, 12H); ^{13}C (75 MHz, $CDCl_3$, APT): δ = 152.6 (C), 148.4 (CH), 135.7 (CH), 128.8 (CH), 118.4 (CH), 115.6 (CH), 114.8 (CH), 83.1 (C), 44.3, 24.7; IR ($CHCl_3$ cast): ν = 2977, 2926, 1651, 1611, 1552, 1457, 1215, 1030, 897, 668, 648 cm^{-1}; HRMS (ES): m/z calcd for $C_{16}H_{23}BN_2O_2$: 286.1931; found 287.1938 $[M+H]^+$.

3.4.2 General solution-phase procedure for the preparation of bicyclic piperidine products 2a-2o, and 16

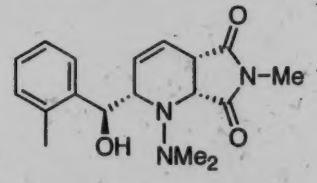
To a solution of diene **10** (1 or 2 equiv) in toluene (5 mL) was added aldehyde (1 equiv) under a nitrogen atmosphere at room temperature. The dienophile (1 or 2 equiv) was added to the above mixture which was then heated at 80° C for 3 days, then allowed to cool down to RT, diluted with EtOAc, and stirred for 30 minutes in a saturated solution of sodium hydrogen carbonate. The organic layer was separated, and the aqueous layer was extracted three times with EtOAc (15 mL each). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated to afford **14** as a crude product. Purification by flash column chromatography using 1% MeOH in dichloromethane (or EtOAc/hexanes system) led to the isolation of the pure alcohol **2** as pale yellow solid in 42-77% yield (see Table 3.1).

Rac-(*2R, 4αR,7αR*)-1-Dimethylamino-2-[(*R*)-hydroxyphenylmethyl]-6-phenyl-4a-7a-dihydro-1H-pyrrolo[3,4-b]pyridine-5,7-(2H, 6H)dione (2a)



Pale yellow solid (0.48 g, 50%); m.p. 80-82 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25-7.55 (m, 10H), 6.01 (ddd, J = 1.5, 3.7, 10.5 Hz, 1H), 5.75 (ddd, J = 1.5, 4.3, 10.6 Hz, 1H), 4.62 (d, J = 8.4 Hz, 1H), 4.24 (br s, 1H, OH), 3.89 (d, J = 9.5 Hz, 1H), 3.62-3.58 (m, 1H), 3.54-3.48 (m, 1H), 2.50 (s, 6H); ^{13}C (75 MHz, $CDCl_3$, APT): δ = 176.1, 174.0(CO), 140.1, 131.6 (C), 130.6, 129.2, 128.7, 128.5, 128.2, 127.2, 126.3, 121.1, 76.6, 61.4, 57.2, 43.7 (N-CH_3), 38.9 (CH); IR ($CHCl_3$ cast): ν = 3475, 2944, 1783, 1597, 1454, 1199, 1059, 864, 667, 646, 621 cm^{-1}; MS (ES): *m/z* 400 [*M*+Na]$^+$, 378 [*M*+H]$^+$, 360[*M*-H_2O]$^+$; HRMS (ES): *m/z* calcd for $C_{22}H_{23}N_3O_3$ 377.1637; found 400.1639 [M+Na]$^+$.

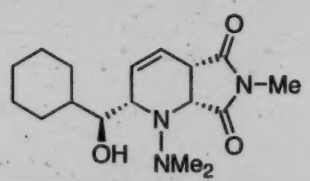
Rac-(*2R, 4aR,7aR*)-1-Dimethylamino-2-[(*R*)-hydroxy(2-methylphenyl)methyl]-6-methyl-4α,7α-dihydro-1H-pyrrolo[3,4-b]pyridine-5,7-(2H, 6H)dione (2e)



Yellow solid (0.17 g, 50%); m.p. 182-183 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50 (dd, J = 1.2, 8.7 Hz, 1H), 7.20 (dd, J = 1.2, 6.8 Hz, 1H), 7.13 (dt, J = 1.5, 7.5 Hz, 1H), 7.04 (d, J = 7.2 Hz, 1H), 5.85 (ddd, J = 1.5, 3.9, 10.5 Hz, 1H), 5.6 (ddd, J = 2.1, 4.7, 10.5 Hz,

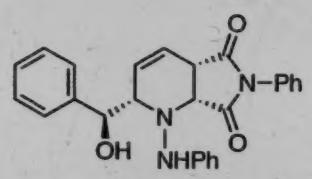
1H), 4.50 (d, J = 8.4 Hz, 1H), 4.1 (d, J = 9.9 Hz, 1H), 3.55-3.50 (m, 1H), 3.47-3.39 (m, 1H), 3.05 (s, 3H), 2.50 (s, 6H), 2.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.1, 175.0, 138.3, 135.3, 130.4, 130.2, 127.7, 126.6, 126.5, 70.4, 61.4, 57.2, 43.8, 38.7, 25.2, 19.4; FTIR ($CHCl_3$ cast): ν = 3471, 2946, 2817, 2776, 1780, 1705, 1434, 1374, 1279 cm^{-1}; HRMS (EI): m/z calcd for $C_{18}H_{23}N_3O_3$ 329.1740; found 329.1741 $[M]^+$; elemental analysis calcd (%) for $C_{18}H_{23}N_3O_3$ (329.17): C, 65.65, H, 6.99, N, 12.76, found C, 65.52, H, 6.92, N, 12.62.

Rac-(*2R, 4aR,7aR*)-1-Dimethylamino-2-[(*S*)-hydroxycyclohexylmethyl]-6-methyl-4α,7α-dihydro-1H-pyrrolo[3,4-b]pyridine-5,7-(2H, 6H)dione (2g)



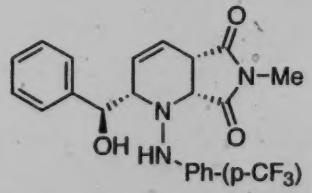
Orange solid (0.12 g, 39%); m.p. 162-164 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.05 (ddd, J = 2.1, 4.8, 10.5 Hz, 1H), 5.94 (ddd, J = 1.2, 3.9, 10.5 Hz, 1H), 4.38 (d, J = 8.7 Hz, 1H), 3.48-3.42 (m, 2H), 3.40-3.36 (m, 1H), 2.95 (s, 3H), 2.60 (d, J = 9 Hz, 1H), 2.48 (s, 6H), 1.78-1.09 (five m's, 11H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.2, 175.1, 130.7, 121.1, 76.1, 56.7, 43.6, 39.1, 38.6, 31.2, 26.8, 26.4, 25.3, 25.2; IR ($CHCl_3$ cast): ν = 3495, 2927, 2851, 2772, 1781, 1705, 1434, 1376, 1278 cm^{-1}; HRMS (EI): m/z calcd for $C_{17}H_{27}N_3O_3$ 321.2052; found 321.2058 $[M]^+$; elemental analysis calcd (%) for $C_{17}H_{27}N_3O_3$ (321.20): C, 63.55, H, 8.41, N, 13.03, found C, 63.57, H, 8.49, N, 13.07.

Rac-(*2R, 4aR,7aR*)-1-Phenylamino-2-[(*R*)-hydroxyphenylmethyl]-6-phenyl-4α,7α-dihydro-1H-pyrrolo[3,4-b]pyridine-5,7-(2H, 6H)dione (2i)



Pale yellow solid (0.32 g, 76%); m.p. 204-206° C; ^{1}H NMR (300 MHz, $CDCl_3$+D_2O): δ = 7.49-6.92 (m, 15H), 6.23-6.17 (m, 1H), 5.59 (ddd, J = 2.2, 4.4, 10.4 Hz, 1H), 4.61 (d, J = 9.2 Hz, 1H), 4.22 (d, J = 9.6 Hz, 1H,), 3.91 (br s, 1H, OH), 3.85-3.71 (m, 2H); ^{13}C (75 MHz, CD_2Cl_2): δ = 173.6, 173.5 (CO), 147.1 139.4, 131.3 (C), 129.6, 129.4, 129.3, 129.1, 128.6, 128.4, 127.1, 126.2, 126.1, 121.1, 114.13, 76.3, 68.1, 68.0, 38.3 (CH); IR ($CHCl_3$ cast): ν = 3515, 3028, 2920, 1715, 1600, 1495, 1454, 1384, 1371, 1247, 1195, 1058, 971, 828, 751, 699 cm^{-1}; MS (ES): m/z 448 [M+Na]$^+$; HRMS (ES): m/z calcd for $C_{26}H_{23}N_3O_3$: 425; found 448.1636 [M+Na]$^+$; elemental analysis calcd (%) for $C_{26}H_{23}N_3O_3$ (425.17): C 73.5, H 5.4, N 9.9, found C 73.2, H 5.2, N 9.6.

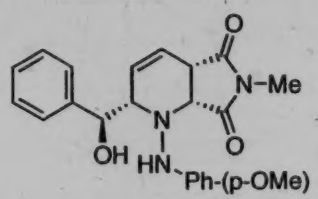
Rac-(*2R, 4aR,7aR*)-1-(4-Trifluoromethylphenyl)amino-2-[(*R*)-hydroxyphenylmethyl]-6-methyl-4α,7α-dihydro-1H-pyrrolo[3,4-b]pyridine-5,7-(2H, 6H)dione (2j)



(0.29 g, 77%); ^{1}H NMR (300 MHz, CD_3COCD_3): δ = 7.48 (d, J = 8.6, 2H), 7.45-7.21 (m, 5H), 7.16 (d, J = 8.3 Hz, 2H), 6.03 (ddd, J = 1.3, 4.4, 10.4 Hz, 1H), 5.58 (ddd, J = 2.2, 4.4, 10.5 Hz, 1H), 4.50 (d, J = 8.2 Hz, 1H), 4.26 (s, 1H), 4.21 (br s, 1H), 3.75-3.58 (m,

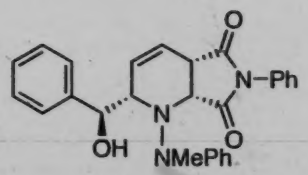
2H), 2.97 (s, 3H); ^{13}C NMR (75 MHz, CD_3COCD_3): δ = 176.6, 175.3, 151.6, 141.6, 128.8, 128.4, 127.9, 126.9, 123.0, 120.4 (q), 113.3, 113.2, 76.2, 76.1, 62.3, 38.0, 25.1; FTIR ($CHCl_3$ cast): ν = 3464, 3246, 2920, 1958, 1784, 1705, 1617, 1527, 1495, 1431, 1413, 1385, 1275 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{22}H_{20}F_3N_3O_3$ 431.1457; found 431.1471 $[M]^+$; elemental analysis calcd (%) for $C_{22}H_{20}F_3N_3O_3$ (431.15): C 61.25, H 4.64, N 9.74, found C 61.1, H 4.51, N 9.64.

Rac-(*2R, 4aR,7aR*)-1-(4-Methoxyphenyl)amino-2-[(*R*)-hydroxyphenylmethyl] -6-methyl-4α,7α-dihydro-1H-pyrrolo[3,4-b]pyridine-5,7-(2H, 6H)dione (2k)



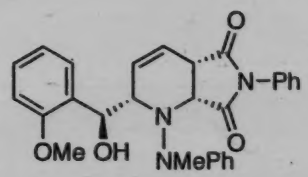
pale yellow solid (0.19 g, 55%); m.p. 210° C (decomposition); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25-7.12 (m, 5H), 6.97-6.92 (m, 2H), 6.82-6.76 (m, 2H), 6.15-6.05 (m, 1H), 5.45 (ddd, *J* = 2.2, 4.7, 10.4 Hz, 1H), 4.39 (d, *J* = 8.3 Hz, 1H), 4.09-3.95 (m, 1H), 3.71 (s, 3H), 3.58 (m, 1H), 3.54-3.44 (br s, 1H), 3.00 (s, 3H); ^{13}C (75 MHz, $CDCl_3$): δ = 174.7 (CO), 154.7 (C), 139.5 (C), 128.5 (CH), 128.3 (CH), 127.1 (CH), 116.0 (CH), 114.9 (CH), 67.3 (CH), 55.7 (CH_3), 37.6 (CH), 25.3 (CH_3); IR (CH_2Cl_2 cast): ν = 2827, 1771, 1604, 1299, 1205, 1167, 995, 918, 902, 878, 677, 619, 599, 561 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{22}H_{23}N_3O_4$ 393.1700; found 393.1704 $[M]^+$; elemental analysis calcd (%) for $C_{22}H_{23}N_3O_4$ (393.44): C, 67.16, H, 5.89, N, 10.68, found C, 66.63, H, 5.78, N, 10.62.

Rac-(*2R, 4aR,7aR*)-(1-Methylphenylamino)-2-[(*R*)-hydroxyphenylmethyl]-6-phenyl-4α,7α- dihydro-1H-pyrrolo[3,4-b]pyridine-5,7-(2H, 6H)dione (21)



Pale yellow solid (0.625 g, 65%); m.p. 190-192° C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60-7.20 (m, 15H), 6.10 (ddd, J = 1.5, 3.5, 9.0 Hz, 1H), 5.81 (ddd, J = 2.4, 4.1, 10.6 Hz, 1H), 4.41 (d, J = 8.3 Hz, 1H), 4.20 (d, J = 8.9 Hz, 1H), 3.96 (br s, 1H, OH), 3.71-3.62 (m, 2H), 3.01 (s, 3H); ^{13}C (75 MHz, $CDCl_3$): δ = 175.7, 173.6 (CO), 149.3, 139.8, 131.3 (C), 131.0, 129.5, 129.3, 128.9, 128.5, 128.2, 127.1, 126.0, 120.1, 114.4, 76.6, 66.3, 58.6, 39.5 (CH), 35.6 (CH_3); IR ($CHCl_3$ cast): ν = 3497, 2921, 1716, 1597, 1496, 1454, 1384, 1371, 1244, 1141, 971, 829, 792, 692, 622 cm^{-1}; MS (ES)): m/z calcd for $C_{27}H_{25}N_3O_3$: 462, found 485.1 $[M+Na]^+$.

Rac-(*2R, 4aR,7aR*)-(1-Methylphenylamino)-2-[(*R*)-hydroxy(2-methylphenyl)methyl] -6-phenyl-4α,7α-dihydro-1H-pyrrolo[3,4-b]pyridine-5,7-(2H, 6H)dione (2m)



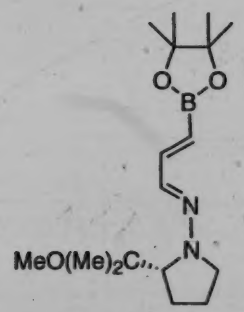
Light orange solid (0.35 g, 68%); m.p. 196-198 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50-7.36 (m, 4H), 7.32-7.18 (m, 7H), 6.94 (dd, J = 7.5, 7.5 Hz, 1H), 6.88-6.82 (m, 1H), 6.80 (d, J = 8.3 Hz, 1H), 6.05 (ddd, J = 1.8, 3.9, 10.5 Hz, 1H), 5.80 (ddd, J = 1.8, 4.5,

10.5 Hz, 1H), 4.80 (dd, J = 2.4, 8.1 Hz, 1H), 4.40 (d, J = 8.4 Hz, 1H), 3.79-3.71 (m, 1H), 3.66-3.58 (m, 1H), 3.62 (s, 3H), 3.56 (br d, J = 2.7 Hz, 1H), 3.00 (s, 3H); ^{13}C (75 MHz, $CDCl_3$, APT): δ = 175.9, 173.9, 156.2, 149.4, 131.6, 131.0, 129.3, 129.2, 128.8, 128.3, 127.3, 126.3, 120.9, 120.6, 119.7, 114.2, 110.4, 68.8, 65.5, 58.8, 55.2, 39.2, 35.5; IR ($CHCl_3$ cast): ν = 3524, 3061, 2937, 1782, 1716, 1598, 1494, 1464, 1387, 1371 cm^{-1}; HRMS (EI): m/z calcd for $C_{28}H_{27}N_3O_4$: 469.2002; found 469.1998 $[M]^+$; elemental analysis calcd (%) for $C_{28}H_{27}N_3O_4$ (469.53): C 71.61, H 5.75, N, 8.95; found C 71.82, H 5.63, N 8.72.

3.4.3 Procedure for the preparation of diene 15.

This compound was prepared using a procedure previously reported by Hall and Tailor.[1] To a solution of aldehyde **1** (0.35 g, 1.90 mmol, 1 equiv) in anhydrous Et_2O (20 mL) was added a catalytic amount of glacial acetic acid (1 drop) followed by SADP (0.60 g, 3.8 mmol, 2 equiv). After vigorous stirring for 1 h at reflux, the mixture was extracted with water (2 × 10 mL). The organic layer was washed once with a saturated aqueous solution of sodium chloride, then dried with anhydrous magnesium sulfate, filtered and concentrated to give the chiral heterodiene **15** as a pale yellow solid (0.57 g, 93%). The crude material was subjected immediately to the tandem [4+2]/allylboration reaction.

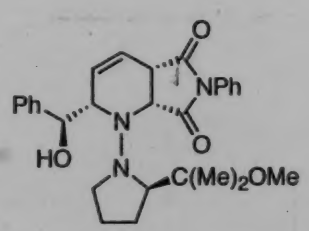
1-[(2R) 2-(methoxy-diphenyl-methyl)-pyrrolidin-1-yl]-1-aza-(3*E*)1,3-butadienyl]-4,4,5,5-tetramethyl-1,3,2- dioxaborolane



Yellow oil (92%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.11 (dd, J = 9.1, 17.9 Hz, 1H), 6.93 (d, J = 8.9 Hz, 1H), 5.46 (d, J = 17.9 Hz, 1H), 3.34-3.31 (m, 1H), 3.21 (s, 3H), 2.50-2.20 (m, 2H), 1.91-1.53 (m, 4H), 1.23 (s, 12H), 1.12 (s, 3H), 1.11 (s, 3H); ^{13}C (75 MHz, $CDCl_3$, APT): δ = 149.4 (CH), 148.9 (CH), 135.1 (CH), 83.3 (C), 82.3 (C), 76.0 (CH), 48.9 (CH_2), 26.7 (CH_2), 23.2, 22.1 (CH_3), 22.0 (CH_3), 21.7 (CH_2), 19.4 (CH_3); IR ($CHCl_3$ cast): ν = 2975, 2933, 2826, 1468, 1213, 924, 667, 647 cm^{-1}; MS (ES): m/z 323 $[M+H]^+$; HRMS (ES): m/z calcd for $C_{17}H_{31}BN_2O_3$: 322.2506; found 323.2500 $[M+H]^+$.

***2R, 4aR,7aR*)-[(*2R*) 2-(Methoxy-diphenyl-methyl)-pyrrolidin-1-yl]-2-[(*R*)-hydroxy-phenylmethyl]-6-phenyl-4α,7α-dihydro-1H-pyrrolo[3,4-b]pyridine-5,7-(2H,6H)dione (15)**

This compound was prepares according to the general procedure described above (section 3.4.2).



Yield (0.5 g, 55%); m.p. 80-82° C; ^{1}H NMR (300 MHz, $CDCl_3$): *d* = 7.48-7.22 (m, 10H), 6.01 (ddd, *J* = 1.6, 3.7, 10.6 Hz, 1H), 5.70 (ddd, *J* = 2.3, 4.5, 10.5 Hz, 1H), 5.38 (s, 1H), 4.80 (d, *J* = 8.5 Hz, 1H), 4.01 (d, *J* = 9.6 Hz, 1H), 3.63-3.60 (m, 1H), 3.38-3.28 (m, 2H), 3.36 (s, 3H), 2.92-2.88 (m, 1H), 2.65-2.61 (m, 1H), 1.78-1.71 (m, 1H), 1.68-1.57 (m, 3H), 1.37 (s, 3H), 1.18 (s, 3H); ^{13}C (75 MHz, $CDCl_3$, APT): δ = 175.2, 174.1 (CO), 140.7, 131.7, 130.8, 129.3, 128.8, 128.4, 128.1, 127.2, 126.3, 122.1, 78.5 (C), 76.1, 67.9, 63.2, 60.0, 50.7, 49.1 (CH), 38.4, 25.8, 22.7 (CH_2), 21.9, 20.6 (CH_3); IR ($CHCl_3$ cast): ν = 3853, 2932, 1715, 1651, 1597, 1499, 1455, 1382, 1179, 1142, 753, 692, 667, 621 cm^{-1}; MS (ES): *m/z* found for $C_{28}H_{33}N_3O_4$: 475.25; found 476.3 $[M+H]^+$.

3.5 References

(1) Tailor, J.; Hall, D. G. *Org. Lett.* **2000**, *2*, 3715-3718.

(2) Eugster, C. H. *Heterocycles* **1976**, *4*, 51-105.

(3) For a review of the isolation, syntheses and biological activities of indozilidine alkaloids, see: Michael, J. P. *Natural Product Reports* **2003**, *20*, 458-475.

(4) Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515-553.

(5) Truscheit, E.; Hillebrand, I.; Junge, B.; Müller, L.; Puls, W.; Schmidt, D. *Prog. Clin. Biochem. Med.* **1988**, *7*, 17-99.

(6) Laver, W. G.; Bischofberger, N.; Webster, R. G. *Sci. Am.* **1999**, *Jan*, 78-87.

(7) For recent reviews on multicomponent reactions, see: (a) Weber, L.; Illgen, K.; Almstetter, M. *Synlett* **1999**, 366-374. (b) Dömling, A. *Comb. Chem. & High*

Through. Screen. **1999**, *1*, 1. (c) Dömling, A.; Ugi, I. *Angew. Chem.* **2000**, *112*, 3300-3344; *Angew. Chem. Int. Ed.* **2000**, *39*, 3169-3210. (d) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321-3329. (e) Zhu, J. P. *Eur. J. Org. Chem.* **2003**, 1133-1144.

(8) For reviews on the synthesis of piperidine-containing natural products, see: (a) Casiraghi, G.; Zanardi, F.; Rassu, G.; Spanu, P. *Chem. Rev.* **1995**, *95*, 1677-1716; (b) Michael, J.P. *Nat. Prod. Rep.* **1998**, 571-594. c) Bailey, P.D.; Millwood, P.A.; Smith, P.D. *Chem. Commun.* **1998**, 633-640. d) Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2553-2581. e) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781.

(9) Grieco, P. A.; Bahsas, A. *Tetrahedron Lett.* **1988**, *29*, 5855-5858.

(10) (a) Maison, W.; Lützen, A.; Kosten, M.; Schlemminger, I.; Westerhoff, O.; Martens, J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3515-3525. (b) Maison, W.; Lützen, A.; Kosten, M.; Schlemminger, I.; Westerhoff, O.; Saak, W.; Martens, J. *J. Chem. Soc., Perkin Trans. 1*, **2000**, 1867-1871. (c) González-Zamora, E.; Fayol, A.; Bois-Choussy, M.; Chiaroni, A.; Zhu, J. *Chem. Commun.* **2001**, 1684-1685.

(11) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798-11799.

(12) (a) Semple, J. E.; Owens, T. D.; Nguyen, K.; Levy, O. E. *Org. Lett.* **2000**, *2*, 2769-2772; (b) Banfi, L.; Guanti, G.; Riva, R. *Chem. Commun.* **2000**, 985-986; (c) Owens, T. D.; Semple, E. J. *Org. Lett.* **2001**, *3*, 3301-3304; (d) Banfi, L.; Guanti, G.; Riva, R.; Basso, A.; Calcagno, E. *Tetrahedron Lett.* **2002**, *43*, 4067-4069.

(13) Southon, W.; Buckingham, J. Eds., *Dictionary of Alkaloids*, Chapman and Hall: London, UK, New York, NY, **1989**.

(14) Six, Y.; Lallemand, J. -Y. *Tetrahedron Lett.* **1999**, *40*, 1295-1296.

(15) See Figures 3 and 4 and accompanying text in: Ragnarsson, U. *Chem. Soc. Rev.* **2001**, *30*, 205-213.

(16) (a) Hoffmann, R. W.; Brückner, D.; Gerusz, V. J. *Heterocycles* **2000**, *52*, 121-124. (b) Hoffmann, R. W.; Brückner, D. *New J. Chem.* **2001**, *25*, 369-373.

(17) For a review on allylboration chemistry, see: Matteson, D.S. *Stereodirected Synthesis with Organoboranes*, Springer: Berlin, **1995**, Chapter 7.

(18) Data (excluding structure factors) for this structure were obtained by Jyoti Tailor and have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-145481.

(19) Vaultier, M.; Truchet, F.; Carboni, B.; Hoffmann, R.W.; Denne, I. *Tetrahedron Lett.* **1987**, *28*, 4169-4172.

(20) Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron* **2002**, *58*, 2253-2359.

(21) Beaudegnies, R.; Ghosez, L. *Tetrahedron: Asymmetry* **1994**, *5*, 557-560.

(22) The absolute stereochemistry of **11** was assigned tentatively on the basis of Reference 21.

(23) Wang, X. *J. Chem. Soc., Chem. Commun.* **1991**, 1515-1516.

(24) Garnier L.; Plunian, B.; Mortier, J.; Vaultier, M. *Tetrahedron Lett.* **1996**, *37*, 6699-7000.

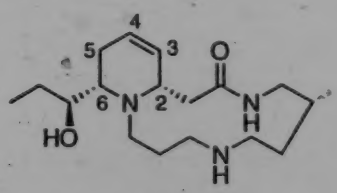
(25) Tailor J. *M.Sc. Thesis*, University of Alberta, Edmonton, Alberta **2000**.

Chapter 4

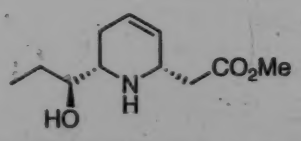
Three-Component Aza[4+2]cycloaddition/Allylboration/Retro-sulfinyl-ene Sequential Reaction: a New Stereocontrolled Entry to Palustrine Alkaloids and Other 2,6-Disubstituted Piperidines

4.1 Introduction

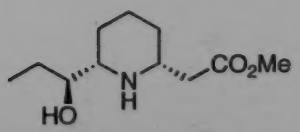
Following the successful studies discussed in Chapter 3, we were interested in the challenge of adapting our tandem aza[4+2]cycloaddition/allylboration reaction to access 2,6-disubstituted piperidine units[1] such as those featured in the palustrine class of alkaloids exemplified by palustrine itself (**1**), methyl palustramate (**2**), and the saturated degradation product methyl dihydropalustramate (**3**) (Figure 4.1).



(+)-palustrine (**1**)



(–)-methyl palustramate (**2**)



(–)-methyl dihydropalustramate (**3**)

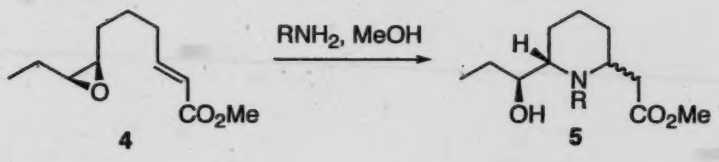
Figure 4.1. Palustrine alkaloids.

Palustrine (**1**) is a toxic component of the horsetail plant *Equisetum paluster L.* found in the moist meadows of Europe.[2] Its reported biological effects include the loss of appetite, weight loss, and decreased milk secretion on grazing animals, particularly cows.[3] Methyl palustramate (**2**) is a postulated biosynthetic precursor, whereas methyl dihydropalustramate (**3**) constitutes a degradation product. Palustrine represents an interesting synthetic target due to the 2,6-*cis* relationship between the two ring substituents, the isolated double bond, the 13-membered macrocyclic lactam, and most importantly, the presence of a stereodefined α-hydroxyalkyl side chain on the piperidine core. The stereoselective synthesis of the latter motif and the regioselective introduction of the C3-C4 unsaturation indeed represent significant synthetic challenges that have been addressed in the past, albeit the proposed solutions involved tedious linear manipulations as outlined below.

4.2 Synthetic approaches to the α-hydroxyalkyl piperidine motif and efforts towards the synthesis of the palustrine natural product

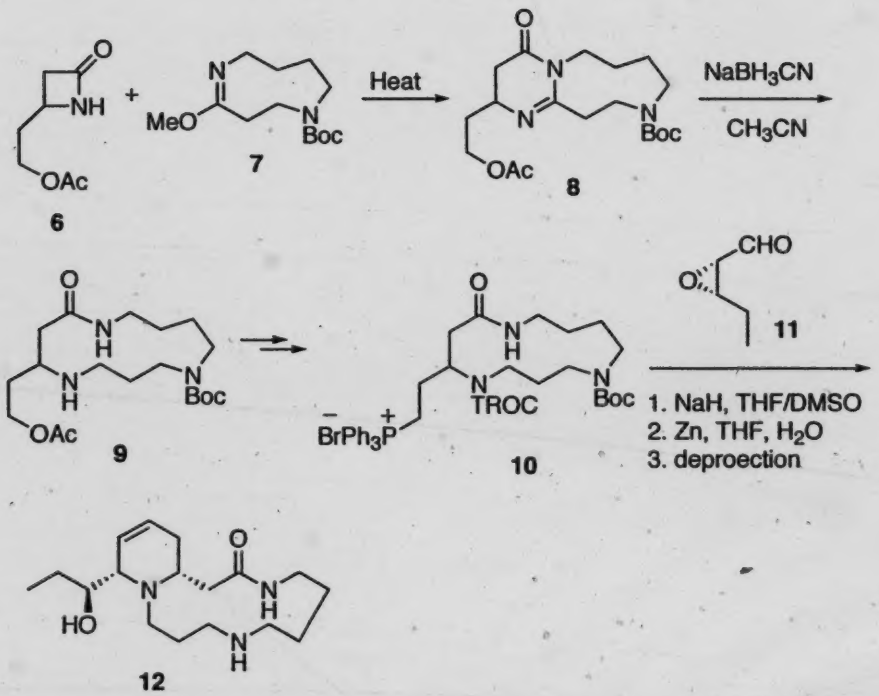
Quinine, a natural product containing an α-hydroxyalkyl piperidine motif,[4] has been known for more than a century. However, the first construction of the latter unit was achieved only a quarter of a century ago by Eugster and co-workers during the course of synthetic studies aimed at elucidating the stereochemistry of palustrine natural product.[5] To this end, substrates of type **4** were prepared via an undisclosed route then treated with various amines to afford the α-hydroalkyl piperidine **5** as a mixture of

diasteromers via a tandem epoxide opening/Michael addition (Equation 4.1). Comparison of spectral data obtained from **5** with those of **3** then allowed the assignment of the relative stereochemistry of **1** as depicted in Figure 4.1.



(4.1)

Following this pioneering exploratory work, the intriguing framework of palustrine (**1**) caught the attention of Wasserman and co-workers. The main contribution from this group remained an innovative approach to the macrocyclic lactam. Indeed, the previously described epoxide opening disconnection was employed to secure the α-hydroalkyl piperidine framework (Scheme 4.1).[6] The synthesis was initiated by heating a reaction mixture containing the four-membered lactam **6** and imidate **7**. Treatment of the resulting compound **8** with sodium cyanoborohydride triggered a ring expansion that completed the efficient construction of the lactam moiety. The product of this reaction **9** was further elaborated into phosphonium salt **10** using a series of standard synthetic manipulations. The latter compound **10** was then carried through the key tandem Wittig condensation/intramolecular nucleophilic epoxide opening to afford derivative **12**. The ^{1}H-NMR spectrum of **12** was not identical to that of the palustrine natural product (**1**). The two compounds (i.e **1** & **12**), however, could be converted to a common intermediate by simple hydrogenation. Altogether, these data were interpreted to mean that the position of the double bond had initially been misassigned in the original palustrine structure.[5]

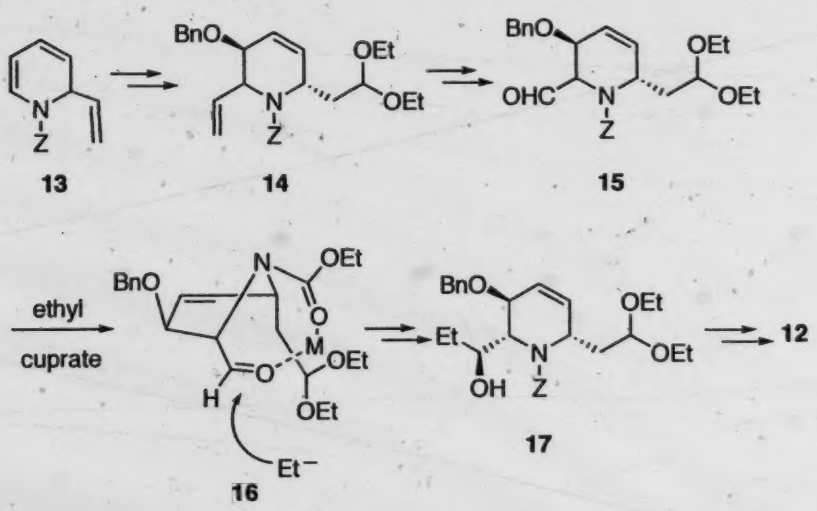


Scheme 4.1. Synthesis of palustrine analogue **12** by Wasserman and co-workers.

The efficiency of this epoxide ring opening strategy to access the α-hydroxyalkyl piperidine unit was also recently highlighted by Jacobsen and co-workers during the course of the asymmetric synthesis of quinine (**32**, Equation 4.2) and quinidine.[7]

The doubt that has been cast over the accuracy of the initially proposed structure of palustrine (**1**) by Wasserman was further corroborated by the studies of Natsume and coworkers on the total synthesis of this natural product (Scheme 4.2).[8] The work of these authors built on their initial finding that the α-hydroxy stereocenter of **1** could be introduced via nucleophilic addition of diethyl cuprate species onto aldehydes such as **15**. The latter substrate was assembled in many steps via a pyridine dearomatization strategy and treated with various copper complexes to afford **17**, which is predominantly as the

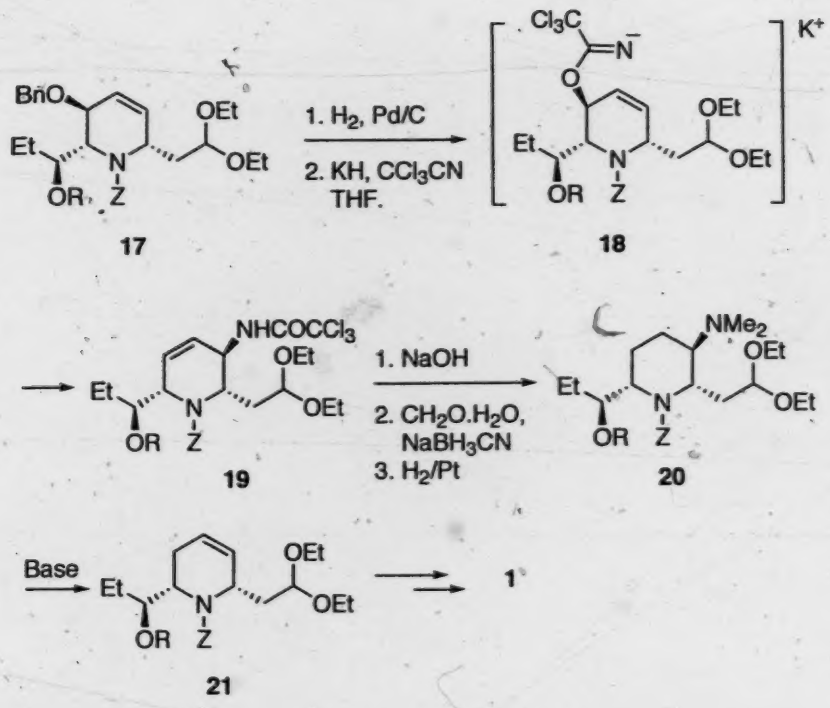
major product albeit in modest yield and diastereomeric ratio. A chelation model **16** was used to rationalize the stereochemical outcome.[9] The macrocycle was built using a series of standard transformations to afford the wrong isomeric structure **12** of palustrine.



Scheme 4.2. Synthesis of palustrine analogue **12** by Natsume and co-workers

The authors then speculated that the double bond was located at the C3-C4 position rather than the proposed C4-C5 position. This compound was constructed from the previous intermediate **17**. First, the alcohol was debenzylated and treated with trichloro acetonitrile in the presence of sodium hydride. The resulting imidate intermediate **18** underwent an allylic transposition to afford **19** (Scheme 4.3). The amide was first deprotected and then methylated, thereby setting the stage for a regioselective, base-promoted elimination to introduce the C3-C4 unsaturation. Compound **19** was elaborated in many steps into target **1**, which was shown to be identical to the natural product. This work constituted the first total synthesis of palustrine (**1**), although racemic.

It also established methyl palustramate (**2**) as a possible synthetic intermediate to palustrine (**1**).[10]

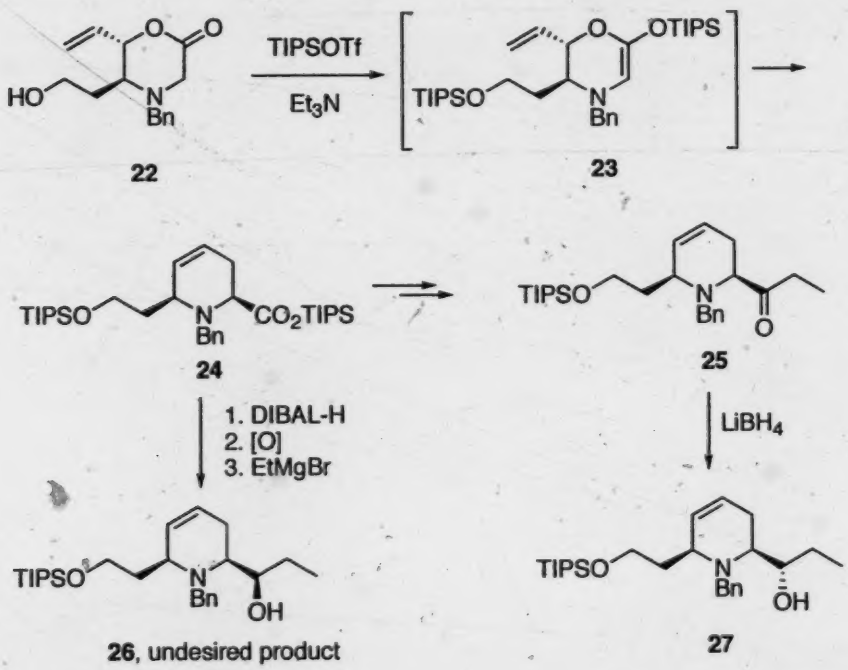


Scheme 4.3. Racemic synthesis of palustrine (**1**) by Natsume and co-workers.

Hirai and co-workers exploited a very similar synthetic strategy to assemble an advanced intermediate towards the asymmetric synthesis of **1**, which however was not completed.[11]

Angle and co-workers reported the first expedient solution to the construction of the double bond in methyl palustramate (**1**) via a restricted Claisen rearrangement strategy.[12] To this end, lactone **22**, obtained in many steps from L-methionine, was first converted to silyl enol ether **23** (Scheme 4.4) and the latter underwent a stereoselective Claisen rearrangement to afford the 2,6-*cis*-piperidine **24** bearing the C3-C4 unsaturation.

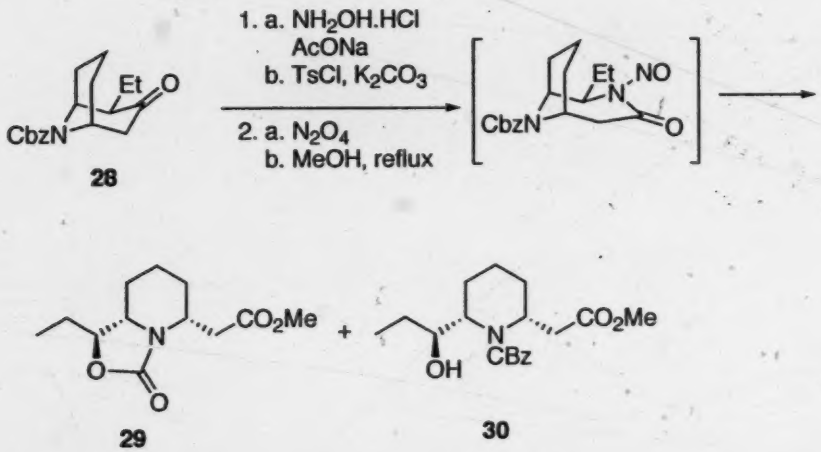
The ester was then reduced to the aldehyde thereby setting the stage for the construction of the hydroxyalkyl stereocenter, which was first attempted via the addition of ethylmagnesium bromide. However, this system did not benefit from the chelate pre-organization effect observed earlier. The Grignard addition afforded mainly the undesired product **26** forcing the authors to resort to a ketone reduction strategy to access intermediate **25**. Further manipulation of **27** delivered (-)-methyl palustramate (**2**).



Scheme 4.4. The restricted Claisen rearrangement approach to **2** by Angle and co-workers.

In addition to the approaches described above, Muraoka and co-workers reported an elegant Huisgen-White rearrangement solution to the stereoselective introduction of the C7-hydroxy center (Scheme 4.5). For this purpose, the advanced bicyclic ketone **28**

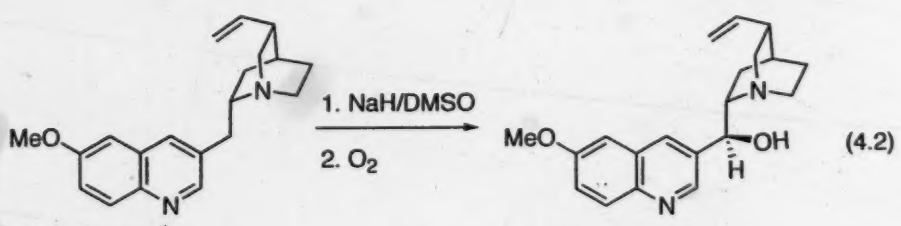
intermediate was submitted to Beckmann rearrangement reaction conditions and the resulting amide was nitrosated. The nitroso intermediate underwent a regio and stereoselective rearrangement, which resulted in the efficient introduction of the secondary alcohol precursor en route to methyl dihydropalustramate (**3**).[13]



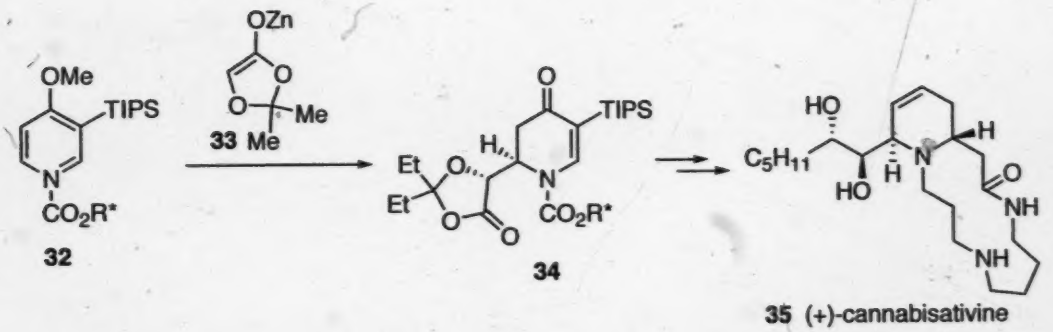
28 **29** **30**

Scheme 4.5. The Beckmann and Huisgen-White rearrangements route to methyl dihydropalustramate by Muraoka and co-workers.

Another approach to the α-hydroxyalkyl piperidine unit includes the benzylic oxidation route disclosed by Stork and collaborators[14] (Equation 4.2), and the asymmetric dearomatization using a zinc enolate **33** by Comins and coworkers (Scheme 4.6).[15]

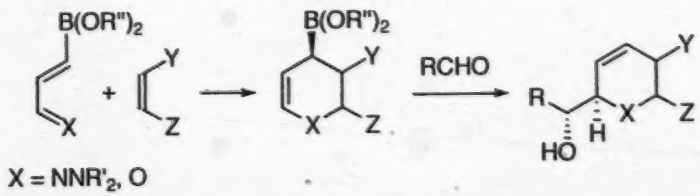


31 **32** quinine (4.2)



Scheme 4.6. Zinc enolate dearomatization route to α-hydroxyalkyl piperidine motif.

In summary, many innovative solutions to the stereocontrolled construction of the α-hydroxyalkyl piperidine motif have been described. However, very few of these approaches truly offer a general solution to the problem. In addition, they are plagued by the number of linear transformations in the elaboration of key synthetic intermediates. Moreover, prior to this work, no convergent MCR strategy was described. Thus, we felt that our three-component tandem hetero[4+2]cycloaddition/allylboration (Scheme 4.7)[16,17] could provide an interesting complementary, if not alternative, solution to these strategies.

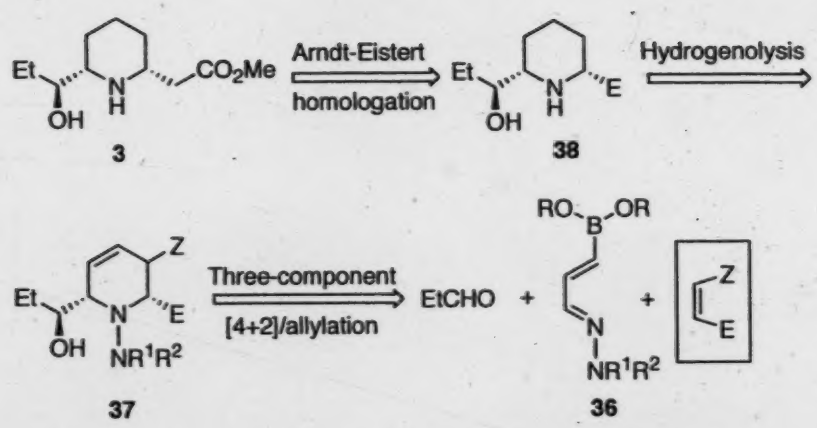


Scheme 4.7. Our three-component aza[4+2]/allylboration route to α-hydroxyalkylated pyrans and piperidines.

As a proof of concept, we chose the palustrine degradation product methyl dihydropalustramate (**3**) as our first target. Our synthetic approach is outlined below.

4.3 Retrosynthetic analysis for methyl dihydropalustramate (3)

Our three-component aza[4+2]cycloaddition/allylboration has shown a very broad substrate scope in terms of hydrazine and aldehyde components (Chapter 3), which makes it particularly suited for applications in diversity-oriented synthesis (DOS).[17] Unfortunately, in the normal electron-demand [4+2] manifold, the bulky electron-withdrawing pinacol boronate substituent exerts a strong deactivating effect on the diene. Thus, the thermal cycloaddition works well only with very electron-poor diactivated dienophiles such as *N*-substituted maleimides; mono-activated dienophiles such as acrylates and vinylsulfones are unreactive. Thus, as targets **1-3** do not bear any substituent at the 3-position (Figure 4.1), their syntheses would require the use of dienophiles bearing easily removable activating groups to overcome the limitations of our methodology with respect to the mitigated reactivity of dienes **36** (Scheme 4.8). However, any such dienophiles would have to meet the following requirements: 1. Possess the requisite electronic characteristics to react with heterodienes **36**. 2. Provide high enantiofacial selectivity. 3. Provide high regioselectivity and lead to a cycloadduct convertible to **3**. The essence of our strategy is captured in Scheme 4.8.

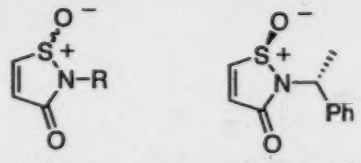


Scheme 4.8. Retrosynthetic analysis for (-)-methyl dihydropalustramate (**3**).

Following the three-component aza[4+2]cycloaddition/allylboration reaction, we envisioned that one of the dienophile's activating groups (Z, Scheme 4.8) could be removed concomitantly with the hydrazine cleavage. Hydrogenolysis using Raney Nickel was identified as a potential method for this task. The synthesis would then be completed via an Arndt-Eistert one-carbon homologation method.

4.4 Results and discussion

With the above criteria in mind, we turned our attention to the 4-isothiazolin-3-one 1-oxide dienophiles (**39**) first reported by Weiler and Brennan.[18]

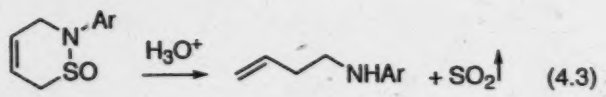


We anticipated that the hydrolysis of the MCR-adduct of these compounds would provide allylic sulfinic acids capable of undergoing a retro-ene fragmentation, thus

providing an efficient desulfurization strategy. This strategy is explained in more details in the next section.

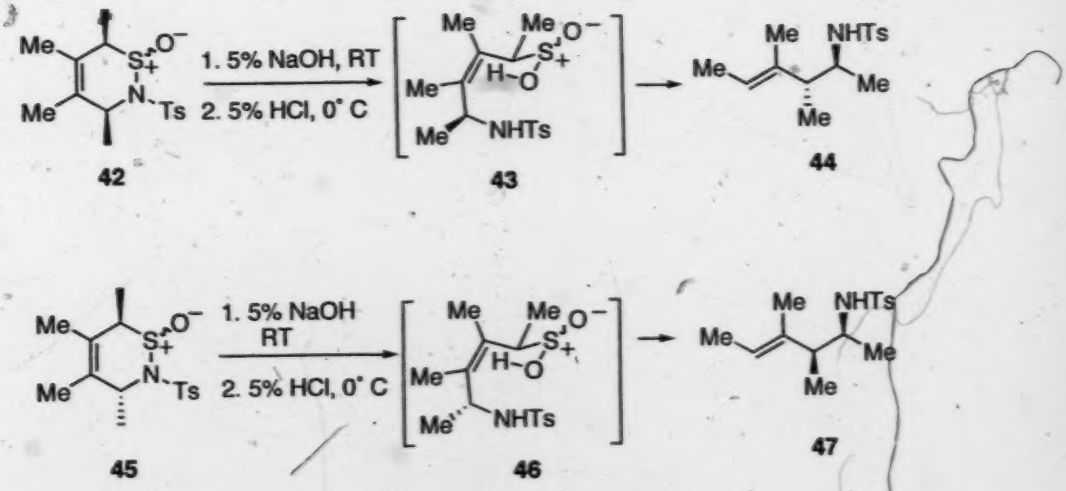
4.4.1 The retro-ene reaction

Allylsulfinic acids are unstable, and rapidly suffer loss of sulfur dioxide concomitant with the migration of the double bond. The first example of this type fragmentation was reported by Wichterle and Rocek in 1953.[19] They demonstrated that compounds of type **40**, obtained by a Diels-Alder reaction, lose sulfur dioxide upon acidification to afford homoallylic amines **41** (Equation 4.3).



40 **41** (4.3)

The reaction was further studied by Wucherpfennig and Kresze,[20] but the exact mechanism has remained elusive prior to work by the group of Mock,[21] which was then further refined by Weinreb.[22] The latter clearly established that the reaction is completely regioselective and stereospecific. For this purpose, substrates **42** and **45** were used to probe the stereo- and regiochemical outcome of the reaction. In both cases, only a single diastereomer and regioisomer of the respective homoallylic amines **44** and **47** were observed (Scheme 4.9). These results are consistent with a concerted mechanism that proceeds via a six-membered transition state whereby the sulfur-bearing carbon controls the facial selectivity of the proton transfer process.



Scheme 4.9. Elucidation of the mechanism of the retro-sulfinyl-ene reaction

4.4.2 Synthetic studies towards methyl dihydropalustramate (3)

To test our hypothesis, sulfinimide dienophiles **39a-d** bearing a variety of substituents on the nitrogen were obtained in excellent yields, and in only three steps following some small modifications to the original procedure.[18] Gratifyingly, these dienophiles reacted smoothly with heterodienes **36** in the presence of aldehydes under our previously optimized reaction conditions (Table 4.1). This process afforded the three-component adducts **48** in moderate to good yield following aqueous sodium bicarbonate work-up and flash chromatography purification. It is remarkable that only one regioisomer and stereoisomer of adducts **48** was observed in the crude reaction mixtures. Obviously, the *endo* pathway operates in the aza-Diels-Alder reaction, and the regiochemistry is controlled by the electron donating 1-amino substituent of the diene along with the carbonyl of the dienophile, which overrides the effect of the sulfoxide group. Moreover, the use of Waldner's dienophile **39b**, obtained from the inexpensive and commercially available optically active *N*-methylbenzylamine,[23] afforded products

that were virtually optically pure. The stereochemical outcome is explained by the *endo* transition structure whereby the diene approaches the dienophile from the face opposite to the S-O bond (Figure 4.2). The aldehyde coordinates to the boron on the *endo* face of the latter adduct to afford **48**. A transition state similar to that proposed in Chapter 3 p. 58 could be account for the stereochemistry of the allylboration step.

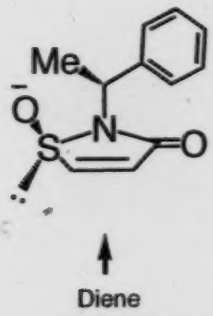
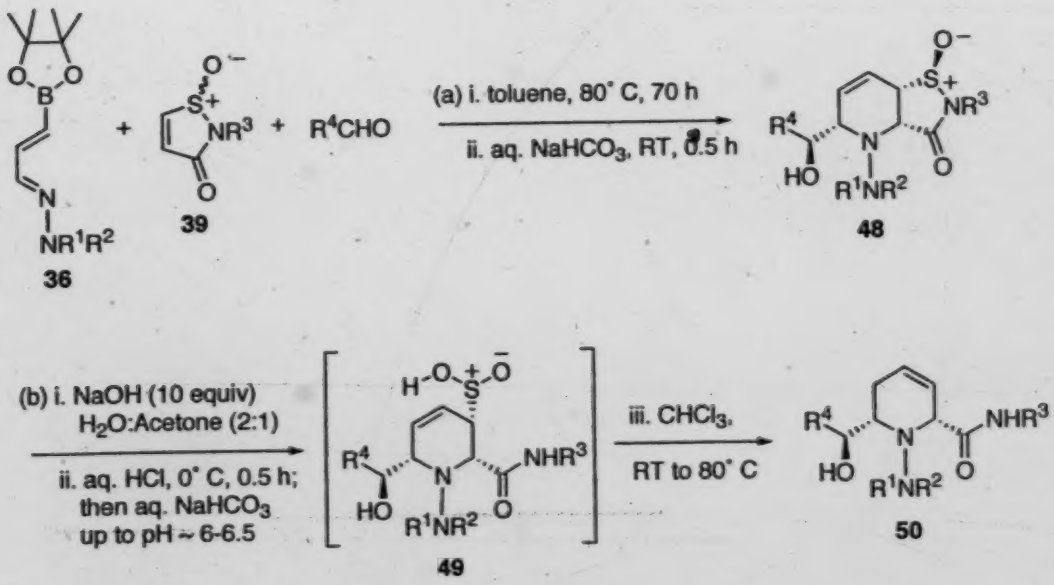


Figure 4.2. Stereochemical rationale for the one-pot Diels-Alder.

To the best of our knowledge, the retro-sulfinyl-ene rearrangement process has never been employed in target-oriented synthesis, and only one study examined cyclic substrates.[24] Thus, our design strategy to 2,6-disubstituted piperidines and the palustrine alkaloids relied on the successful implementation of such a retro-sulfinyl-ene fragmentation involving cyclic adducts **48** from the aza[4+2]/allylboration reaction between dienes **36**, dienophiles **39**, and aldehydes (Table 4.1). In this scenario, SO_2 extrusion from **48** would be concomitant with a migration of the C4-C5 unsaturation to the C3-C4 position, which is necessary for accessing methyl palustramate (**2**).

Table 4.1. Scope of the three-component aza[4+2]/allylboration and retro-sulfinyl-ene fragmentation reaction sequence.[a]


(a) i. toluene, 80° C, 70 h
ii. aq. NaHCO3, RT, 0.5 h
(b) i. NaOH (10 equiv)
H2O:Acetone (2:1)
ii. aq. HCl, 0° C, 0.5 h;
then aq. NaHCO3
up to pH ~ 6-6.5
iii. CHCl3,
RT to 80° C

Entry	Diene			Dienophile		Aldehyde	Product	Yield[b]	Product	Yield[c]
		R^1	R^2		R^3	R^4		(%)		(%)
1	**36a**	Me	Me	**39a**	*t*-Bu	Cy	**48a**	65	**50a**	55
2	**36a**	Me	Me	**39b**[e]	PhCH(Me)	Ph	**48b**	50	**50b**	65
3	**36a**	Me	Me	**39c**	*n*-Pr	Ph	**48c**	51	**50c**	52
4	**36a**	Me	Me	**39d**	PhCH(Me)	*n*-Bu	**48d**	52	**50d**	65
5	**36a**	Me	Me	**39a**	*t*-Bu	Ph	**48e**	49	**50e**	69
6	**36a**	Me	Me	**39a**	*t*-Bu	Et	**48f**	41	**50f**	-[d]
7	**36a**	Me	Me	**39b**	PhCH(Me)	Et	**48g**	44	**50g**	80
8	**36b**	Ph	Me	**39b**	PhCH(Me)	Et	**48h**	41	**50h**	80
9	**36c**	Bn	Bn	**39b**	PhCH(Me)	Et	**48i**	62	**50i**	78
10	**36d**	H	Boc	**39b**	PhCH(Me)	Et	**48j**	0	**50j**	-
11	**36e**	H	Ac	**39b**	PhCH(Me)	Ph	**48k**	0	**50k**	-
12	**36f**	OMe	-	**39b**	PhCH(Me)	Ph	**48l**	0	**50l**	-

[a]All aza[4+2]/allylboration reactions were carried out by heating a 1:1:2 mixture of diene/dienophile/aldehyde, except for propionaldehyde where 5 equivalents were used, in anhydrous toluene [0.2-0.3 M] at 80° C for 70 h. [b]Yields of isolated products after flash chromatography purification. [c]The products were obtained after reflux for 12-48 h in $CHCl_3$ and flash chromatography purification (**48e** was simply stirred at RT). [d]Reaction not attempted. [e] Optically pure dienophile **39b** was used in some cases. [e]Except for 48i, the reactions were perfomed on 200 to 500 mg of the starting material.

In the event, **48e** (entry 5, Table 4.1) was arbitrarily selected for early exploratory work. The latter was submitted to standard retroene reaction conditions consisting of treating the substrate with 5% aq. NaOH, followed by acidification to generate *in situ* the sulfinic acid intermediate **49**. The desired retro-ene product **50e** was obtained, albeit in low yield. To our surprise, when the *t*-butyl group of the dienophile was replaced with the *n*-propyl group **48c** (entry 3, Table 1), no retro-ene product was observed. Likewise, when the aldehyde side chain was replaced with a less sterically demanding group (e.g **48f**, entry 6, Table 1), no product formation was observed either. Longer stirring times in the acidic media or attempt to warm up the solution to room temperature mainly resulted in decomposition. Clearly, an improved retro-ene procedure was required. This was achieved by carefully quenching the acidic solution with a weak base (aqueous $NaHCO_3$) to adjust the pH, followed by removal of the solvent. The sulfinic acid intermediate **48** was then dissolved in chloroform and heated. Only then was the desired product isolated in all cases, although the reaction time and temperature were still a function of the steric bulk of R^3 and R^4. In general, as the size of these groups increase, the reaction time and the temperature required for the reaction to take place can be decreased.

Although the reasons for this reactivity trend remain speculative, conformational effects may be at play to explain the different behavior of **48a-k**. To reach the six-membered transition state for a concerted retro-sulfinyl-ene fragmentation,[23] the sulfinic acid substituent must occupy a pseudo-axial orientation (conformer B) (Figure 4.3). This reactive conformer also features two disfavored gauche interactions between the bulky

hydrazine substituents and both the α-hydroxyalkyl chain and the carboxamide. To minimize this type of strain, closely related *cis*-2,6-disubstituted piperidines have been shown to adopt a "diaxial" conformation (conformer A).[25] In this non-reactive conformer, the carboxamide group occupies a pseudo-axial orientation. Thus, we hypothesize that bulkier *N*-alkyl substituents on the amide may affect the conformational equilibrium and facilitate the retro-ene fragmentation by destabilizing conformer A to the benefit of reactive conformer B.

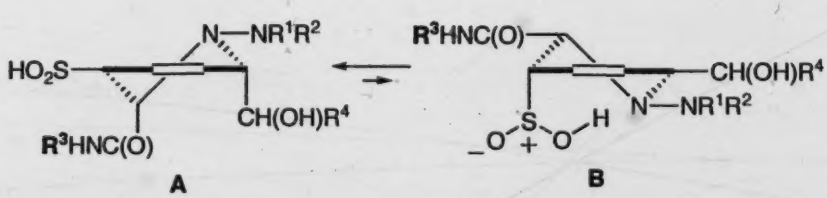
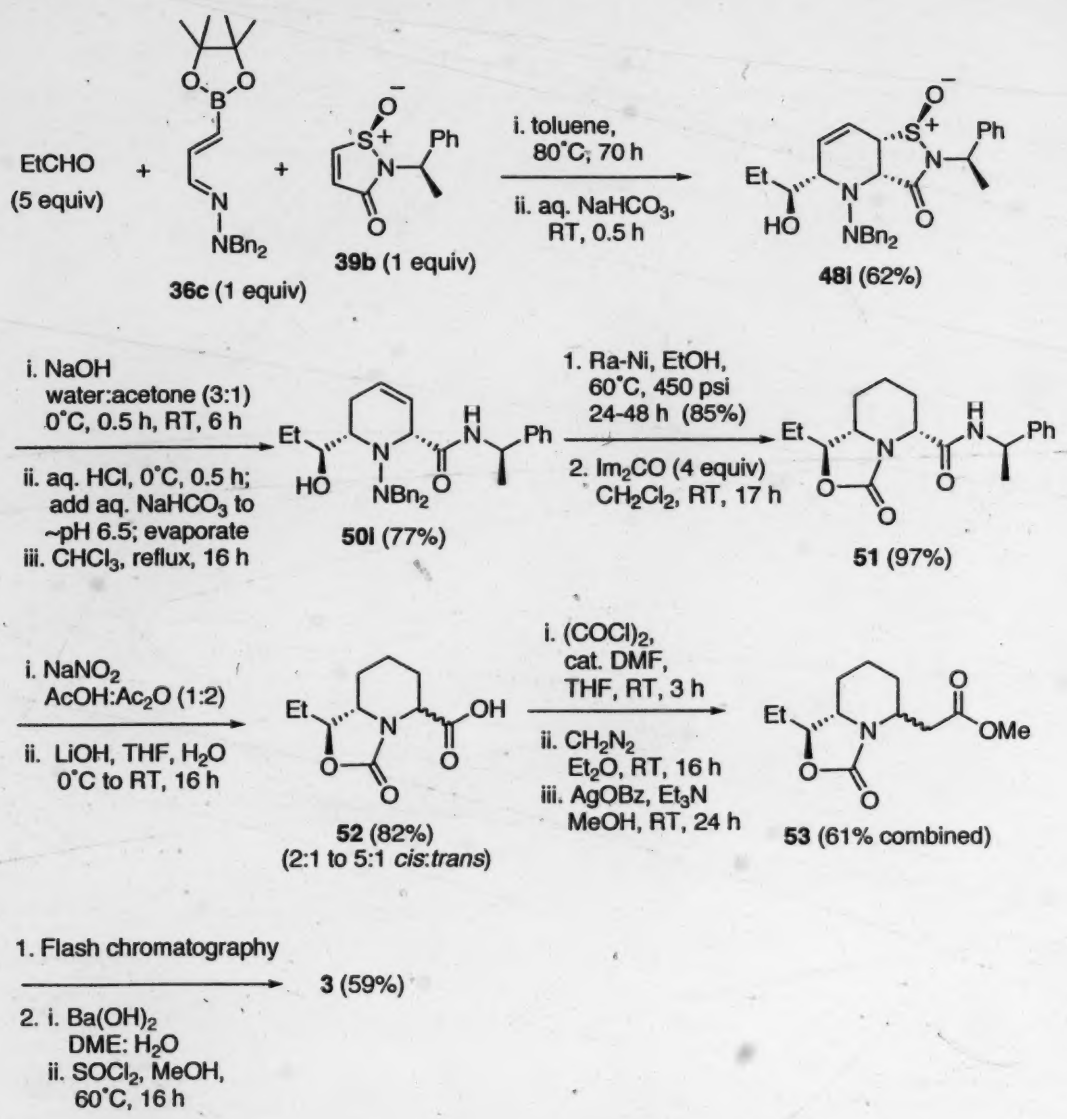


Figure 4.3. Suggested conformational equilibrium to explain the influence of the amide substituent (R^3) of intermediates **49** in the retro-sulfinyl-ene rearrangement.

4.4.3 Completion of the synthesis

We put the applicability of the aza[4+2]/allylboration/retro-sulfinyl-ene sequential reaction to the test by first targeting (-)-methyl dihydroplustramate (**3**) (Scheme 4.10). To this end, we employed 1-dibenzylaminomethyl-1-aza-4-borono-butadiene **36c**, which was prepared easily made from the known 3-boronoacrolein pinacolate, described in chapter 3, through simple dehydrative hydrazone formation with 1,1-dibenzylhydrazine. The key one-pot three-component reaction between equimolar amounts of **36c** and **39b** in the presence of excess propionaldehyde furnished heterobicyclic adduct **48i** as a single regio- and diastereomer in 62% yield. To effect the retro-sulfinyl-ene fragmentation, **48i**

was hydrolyzed and heated as described above. The desired amide product **50i** was isolated in 82% yield, and Ra-Ni promoted hydrogenolysis of the hydrazine, with concomitant reduction of the double bond, was followed by protection of the aminoalcohol to afford the carbamate intermediate **51** in high overall yield. Selective hydrolysis of the amide group of **51** was performed through formation of the *N*-nitroso derivative.[26,27] Unfortunately, in all conditions attempted epimerization occurred in this operation, and the major 2,6-*cis*-configured acid product was always accompanied with variable amounts of the *trans*-isomer. All other methods to hydrolyse this sterically demanding amide failed. Thus, despite the epimerization problem, the *N*-nitrosation strategy provided the best and only route to reach target **3**. The required homologation was performed on the epimeric mixture of carboxylic acids **52** using an Arndt-Eistert sequence. The two isomers were readily separable at that stage and the *cis*- isomer **53** was subjected to the final step of aminoalcohol deprotection. This transformation proved difficult using a known hydrolysis procedure,[13] but we eventually succeeded with the method of Weinreb and co-workers using barium hydroxide.[28] Re-esterification of the resulting amino acid afforded (-)-methyl dihydropalustramate (**3**), which possessed spectral characteristics and optical rotation value in agreement with reported literature data.[13] The entire sequence to reach target **3** was accomplished with very few purification steps, and in only 10 linear synthetic operations from commercially available 3,3′-diethoxypropyne. Further adaptations of this strategy to include a chemoselective N-N cleavage strategy for preserving the C3-C4 unsaturation is expected to allow access to **1** and **2**. Work towards this goal is described in the next chapter.


EtCHO
(5 equiv)
36c (1 equiv)
39b (1 equiv)
i. toluene, 80°C, 70 h
ii. aq. NaHCO3, RT, 0.5 h
48l (62%)
i. NaOH water:acetone (3:1) 0°C, 0.5 h, RT, 6 h
ii. aq. HCl, 0°C, 0.5 h; add aq. NaHCO3 to ~pH 6.5; evaporate
iii. CHCl3, reflux, 16 h
50l (77%)
1. Ra-Ni, EtOH, 60°C, 450 psi 24-48 h (85%)
2. Im2CO (4 equiv) CH2Cl2, RT, 17 h
51 (97%)
i. NaNO2 AcOH:Ac2O (1:2)
ii. LiOH, THF, H2O 0°C to RT, 16 h
52 (82%)
(2:1 to 5:1 cis:trans)
i. (COCl)2, cat. DMF, THF, RT, 3 h
ii. CH2N2 Et2O, RT, 16 h
iii. AgOBz, Et3N MeOH, RT, 24 h
53 (61% combined)
1. Flash chromatography
3 (59%)
2. i. Ba(OH)2 DME: H2O
ii. SOCl2, MeOH, 60°C, 16 h

Scheme 4.10. Total synthesis of the palustrine degradation product (-)-methyl dihydropalustramate (**3**).

4.5 Conclusion

We have described a novel three-component aza[4+2]cycloaddition/allylboration/retro-sulfinyl-ene sequential reaction approach to access *cis*-2,6-disubstituted piperidines in a highly regio- and diastereoselective fashion.

The implementation of the retro-ene reaction proved initially difficult, and was further complicated by the lack of detailed experimental procedure in the literature. Moreover, our studies represent the first retro-ene reaction in the context of a heterocyclic system, and also the first application of this reaction in target-oriented synthesis. The utility of this powerful and step-economical process was successfully demonstrated with a concise enantioselective synthesis of the palustrine degradation product (-)-methyl dihydropalustramate, which to date constitutes the shortest synthetic sequence to this target. Few multicomponent reaction strategies demonstrate such a high level of stereocontrol in the formation of complex, functionalized compounds.

4.6 Experimental

The methods described in section 2.4 of Chapter 2 also apply with the following additions. Except for diene **36c**, the synthesis and characterization data of all other dienes were reported in the experimental section of Chapter 3. Propionaldehyde was always freshly distilled using conventional distillation techniques prior to use. Raney nickel was directly obtained from Aldrich, and tends to gradually lose its activity over time. For compounds **48a-i** and **50a-i**, the reactions yield and scale are reported in Table 4.1 (p.93)

4.6.1 *N*-Nitroso-dibenzylamine

$Bn_2N–NO$

Dibenzylamine (4.0 ml, 21 mmol) was dissolved in 15 mL of THF at room temperature and the *tert*-butyl nitrite was added. The resulting cloudy mixture was refluxed for 17 h then cooled to RT. The solvent was removed under reduced pressure to afford an orange

crystal (4.6 g, 98%)) with sufficient purity to be carried through the next step without further purification.

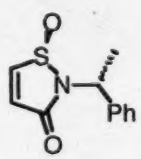
TLC (40% EtOAc/Hexane, UV): 0.74; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38-7.32 (m, 3H), 7.30-7.20 (m, 5H), 7.04-7.02 (m, 2H), 5.19 (s, 2H), 4.63 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 134.5, 133.9, 129.0, 128.8, 128.5, 128.3, 127.8, 60.0, 44.9; IR ($CHCl_3$ cast) ν = 3088, 3064, 3031, 2930, 1956, 1882, 1812, 1677, 1603, 1586, 1496, 1554, 1348, 1317, 1204, 1171, 1157, 1127, 1073, 1029, 1002 cm^{-1}.

4.6.2 *N,N*-Dibenzyl-hydrazine[29]

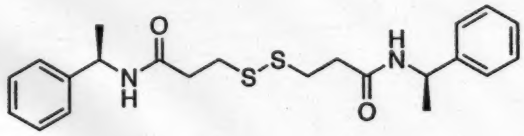
Bn_2N-NH_2

Lithium aluminum hydride (0.54 g, 14.1 mmol) was refluxed in 16 mL of dry ether for one hour. The resulting suspension was cooled to RT then on ice, and a solution of the above *N*-nitroso-dibenzylamine (2.3 g, 10 mmol) in 20 mmol of dry ether was added over one hour via an addition funnel. The reaction mixture was stirred for 1 h, then brought to RT and stirred for an additional hour. Water was added dropwise until the solid precipitates turn completely white. The precipitates were removed by filtration over a celite pad and the filtrate was washed with aqueous 5% NaOH, water and brine successively. The ethereal fraction was dried over magnesium sulfate and evaporated to afford a white solid (1.95 g, 92%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.40-7.28 (m, 10H), 3.73 (s, 4H), 3.02-2.66 (bs, 2H).

4.6.3 (1R)-1-Oxo-2-[(R)-methyl-benzyl]-4,5-dihydro-1-isothiazol-3-one (38b)[30]



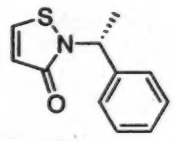
3,3′-dithiodipropionic acid (15.0 g, 71.4 mmol) was dissolved in THF (150 mL) and cooled to 0° C. A catalytic amount of DMF (0.05 mL) was added, followed by oxalyl chloride (12.6 ml, 144.4 mmol), which was added over 20 min. The reaction mixture was stirred on ice until bubbling ceased, and slowly warmed up to RT, and refluxed for 2 h. The mixture was cooled to RT and the solvent was evaporated. The residue was dissolved in 100 mL of THF, and (R)-methyl benzylamine (> 98% ee, 36 ml, 284 mmol) was added slowly over 1 h to avoid any reflux. The resulting white precipitate was left at RT for 2 h and the solvent was evaporated. Water was added and the resulting mixture was stirred for 5 min, diluted with ethyl acetate (100 mL) and transferred to a separatory funnel. The two phases were separated and the aqueous phase was returned to the separatory funnel and extracted two more times with ethyl acetate (50 mL). The combined organic phases were washed with water, brine and 100 ml of hexane was added. The mixture was stirred and maintained at 4° C overnight. A white solid precipitate (dithiodipropionic acid di(methyl-benzyl)amide **S1**, 24.6 g) was recovered by filtration, washed with cold 1:1 ethyl acetate hexane, and dried under vacuum.



S1

To a suspension of **S1** (16.5 g, 40.0 mmol) in 150 mL of toluene was added freshly distilled sulfuryl chloride (9.60 ml, 120 mmol) over 90 min via an addition funnel. The reaction mixture was stirred for 3 h at RT, then 5% aqueous $NaHCO_3$ was added. The mixture was transferred to a separatory funnel and the two phases were separated. The

organic phase was washed with brine, dried over magnesium sulfate and the solvent was evaporated to afford a colorless oil consisting of a mixture of two compounds in ratio varying from (8:1 to 1:1). The two compounds could be separated by flash chromatography. **S2** was obtained as a colorless oil which turns to an off white solid upon standing.



S2

Compound **S2** (7.1 g, 35 mmol) was dissolved in 70 mL of CH_2Cl_2 at 0° C. A solution of mCPBA (8.94 g, 52.2 mmol) in CH_2Cl_2 was slowly added and the mixture was stirred on ice for 3 to 4 h. The white precipitates were removed by filtration and the solvent was evaporated under reduced pressure. Flash chromatography using 30% ethyl acetate/hexane afforded 3.8 g of **39b** as a white solid (major diastereomer) and 1.8 g of a colorless oil (minor diastereomer) (71% combined yield).

TLC (30% EtOAc/ Hexane, UV/ $KMnO_4$): 0.15; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.48 (d, J = 6.3 Hz, 1H), 7.42-7.28 (m, 5H), 6.72 (d, J = 6.4 Hz, 1H), 5.51 (q, J = 7.3 Hz, 1H), 1.82 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.0, 148.5, 139.8, 130.3, 128.9, 128.4, 127.5, 53.2, 19.6; IR ($CHCl_3$ cast) ν_{max} 3380, 3069, 3028, 2992, 2974, 2930, 1958, 1885, 1779, 1705, 1595, 1491, 1283, 1256, 1206, 1156, 1123, 1086 cm^{-1}; elemental Analysis calcd (%) for $C_{11}H_{11}NO_2S$ (221): C 59.72, H 4.98, N 6.33; found: C 59.65, H 4.84 N 6.24

Other dienophiles (**38a**, **38c**, and **38d**) were prepared using the same procedure.

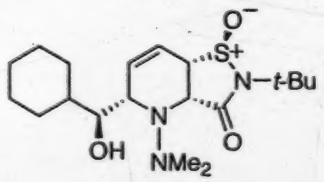
4.6.4 Preparation of the dienes (35)

See experimental section, Chapter 3.

4.6.5 Tandem Diels-Alder/allylboration reaction: typical procedure (cycloadduct 48i)

The dienophile **39b** (1.73 g, 7.80 mmol) was added to a 0.2 M solution of diene **36c** (3.0 g, 7.9 mmol) in toluene. Freshly distilled propionaldehyde (3.1 mL, 39 mmol) was added. The tube was capped and heated to 85° C for 70 h under vigorous stirring. The reaction mixture was allowed to cool to room temperature and saturated $NaHCO_3$ was added. The mixture was stirred for 30 min and the two layers were separated. The aqueous phase was extracted with ethyl acetate (50 mL, twice) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by flash chromatography (silica, 30% ethyl acetate in hexane; 0.2% Et_3N) to afford **48i** (2.6 g, 63 % yield) as an off white solid.

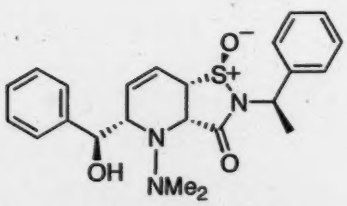
Rac-(*1R,3aR, 5R,7aR*)-1-Dimethylamino-5-[(*S*)-hydroxycyclohexylmethyl]-6-*tert*-butyl-3a,4,5,7a-tetrahydroisothiazolo[3,4-b]pyridin-3-(2H)one-1-oxide (48a)



TLC (50% EtOAc/Hexane, $KMnO_4$/PMA): 0.22; ^1H NMR (500 MHz, $CDCl_3$): δ = 6.11 (ddd, J = 2.5, 3.7, 10.7 Hz, 1H), 5.86 (dm, J = 10.7 Hz, 1H), 4.68 (d, J = 7.0 Hz, 1H), 3.74 (ddd, J = 2.4, 4.9, 7.1 Hz, 1H), 3.56-3.52 (m, 1H), 3.45 (d, J = 4.7 Hz, 1H), 2.72 (dt,

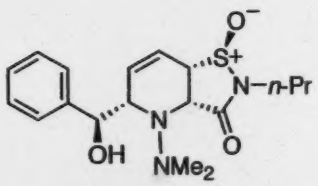
J = 4.5, 7.3 Hz, 1H), 2.40 (s, 6H), 1.80-1.08 (m, 11H), 1.50 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.7, 135.9, 116.4, 76.8, 58.8, 58.4, 57.7, 54.3, 43.1, 39.9, 31.0, 28.4, 26.7, 26.49, 26.46, 26.4, 26.37, 24.9; IR (CH_2Cl_2 cast) ν_{max} = 3488, 2975, 2927, 2852, 2817, 1705, 1452, 1397, 1340, 1290, 1100 cm^{-1}; HRMS (ES): *m/z*: calcd for $C_{19}H_{33}N_3O_3SNa$: 406.2135; found: 406.2136 $[M]^+$

Rac-(*1R,3aR,5R,7aR*)-1-Dimethylamino-5-[(*R*)-hydroxybenzyl]-6-(*1R*-methylbenzyl)-3a,4,5,7a-tetrahydroisothiazolo[3,4-b]pyridin-3-(2H)one-1-oxide (48b)



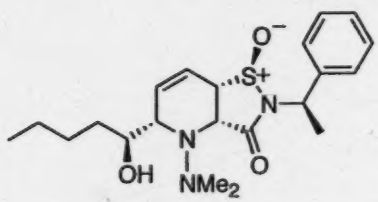
TLC (EtOAc, $KMnO_4$/PMA): 0.32; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.40-7.22 (m, 8H), 7.08-7.02 (m, 2H), 5.75 (dm, *J* = 10.8 Hz, 1H), 5.61 (ddd, *J* = 2.1, 3.9, 10.8 Hz, 1H), 5.52 (q, *J* = 7.2 Hz, 1H), 4.90 (d, *J* = 6.90 Hz, 1H), 4.41 (bs, 1H), 3.83 (ddd, *J* = 2.4, 4.8, 7.2 Hz, 1H), 3.47 (d, *J* = 9.9 Hz, 1H), 3.42-3.34 (m, 1H), 2.48 (s, 6H), 1.84 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.4, 140.5, 140.1, 134.3, 128.8, 128.3, 128.2, 128.0, 127.1, 116,3, 75.1, 62.5, 58.8, 54.9, 54.0, 43.5, 19.9; IR (CH_2Cl_2 cast) ν_{max} = 3475, 3061. 3031, 2981, 2944, 2853, 2818, 2777, 1708, 1495, 1454, 1398, 1383, 1105 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{23}H_{26}DN_3O_3S$: 426.1852; found: 426.1841 $[M]^+$; $[\alpha]_D^{23}$ = -126.15 (c = 5.4 in $CHCl_3$)

Rac-(*1R,3aR,5R,7aR*)-1-Dimethylamino-5-[(*R*)-hydroxybenzyl]-6-*n*-propyl-3a,4,5,7a-tetrahydroisothiazolo[3,4-b]pyridin-3-(2H)one-1-oxide (48c)



TLC (70% EtOAc/Hexane, $KMnO_4$/PMA): 0.22; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38-7.27 (m, 5H), 5.93 (dm, *J* = 10.5 Hz, 1H), 5.82 (ddd, *J* = 2.3, 3.9, 10.8 Hz, 1H), 4.82 (d, *J* = 7.1 Hz, 1H), 4.35 (bs, 1H), 3.87-3.85 (m, 1H), 3.84-3.78 (m, 2H), 3.62-3.52 (m, 1H), 3.53-3.45 (m, 1H), 2.50 (s, 6H), 1.82-1.68 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.9, 140.6, 134.4, 128.4, 128.1, 127.1, 116.6, 75.4, 62.6, 58.5, 54.3, 44.7, 43.5, 21.9, 11.2; IR (CH_2Cl_2 cast) ν_{max} = 3474, 3030, 2936, 2874, 2818, 2776, 1709, 1525, 1495, 1454, 1399, 1325, 1101 cm^{-1}; HRMS (ES): *m/z*: calcd for $C_{18}H_{26}N_3O_3S$: 363.1689; found: 364.1691 $[M+H]^+$

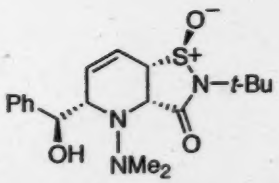
Rac-(*1R,3aR,5R,7aR*)-1-Dimethylamino-5-[(*S*)-hydroxypentyl]-6-(*1R*-methylbenzyl)-3a,4,5,7a-tetrahydroisothiazolo[3,4-b]pyridin-3-(2H)one-1-oxide (48d)



TLC (50% EtOAc, $KMnO_4$/PMA): 0.08; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42-7.21 (m, 5H), 6.07 (ddd, *J* = 2.3, 3.8, 10.7 Hz, 1H), 5.77 (dm, *J* = 10.7 Hz, 1H), 5.44 (q, *J* = 7.1

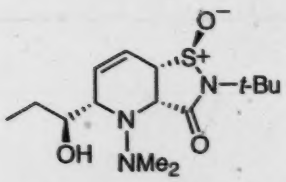
Hz, 1H), 4.80 (d, J = 7.0 Hz, 1H), 3.75 (app dq, J = 2.6, 7.2 Hz, 1H), 3.70 (d, J = 2.4 Hz, 1H), 3.21-3.16 (m, 1H), 2.62-2.57 (m, 1H), 2.43 (s, 6H), 1.80 (d, J = 7.2 Hz, 3H), 1.56-1.38 (m, 3H), 1.38-1.17 (m, 3H), 0.87 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.8, 139.5, 135.1, 128.6, 128.1, 127.1, 116.3, 72.0, 60.9, 58.8, 54.4, 53.9, 43.2, 33.4, 28.0, 24.8, 22.7, 19.6, 14.0; IR (CH_2Cl_2 cast) ν_{max} = 3490, 3032, 2952, 2859, 2818, 2776, 1952, 1708, 1604, 1586, 1496, 1454, 1399, 1379, 1309, 1267, 1014 cm^{-1}; HRMS (ES): *m/z*: calcd for $C_{21}H_{32}N_3O_3S$: 406.2159; found: 406.2162 $[M+H]^+$.

Rac-(*1R,3aR,5R,7aR*)-1-Dimethylamino-5-[(*R*)-hydroxybenzyl]-6-*tert*-butyl-3a,4,5,7a-tetrahydroisothiazolo[3,4-b]pyridin-3-(2H)one-1-oxide (48e)



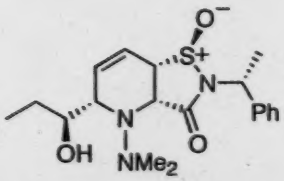
TLC (10% acetone/ether, $KMnO_4$): 0.27; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39-7.28 (m, 5H), 5.89 (dm, J = 10.8 Hz, 1H), 5.78 (ddd, J = 1.6, 3.7, 10.7 Hz, 1H), 4.85 (d, J = 7.0 Hz, 1H), 4.39 (bs, 1H), 3.83 (d, J = 4.4 Hz, 1H), 3.81-3.85 (m, 1H), 3.52-3.46 (m, 1H), 2.52 (s, 6H), 1.62 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.1, 140.7, 134.5, 128.5, 128.1, 127.2, 116.7, 75.8, 63.1, 58.9, 57.6, 55.4, 43.5, 28.6; IR ($CHCl_3$ cast) ν_{max} = 3459, 3036, 3004, 2976, 2941, 2922, 2867, 2822, 2780, 1703, 1604, 1497, 1470, 1455, 1410, 1400, 1369, 1362, 1163, 1060 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{19}H_{28}N_3O_3S$: 378.1852; found: 378.1844 $[M]^+$; Elemental Analysis calcd (%) for $C_{19}H_{28}N_3O_3S$ (378): C 60.47, H 7.16, N 11.14; found: C 60.43, H 7.33, N 11.21.

Rac-(*1R,3aR,5R,7aR*)-1-Dimethylamino-5-[(*S*)-hydroxypropyl]-6-*tert*-butyl-3a,4,5,7a-tetrahydroisothiazolo[3,4-b]pyridin-3-(2H)one-1-oxide (48f)



TLC (7% acetone/ether, $KMnO_4$): 0.25; ^1H NMR (500 MHz, $CDCl_3$): δ = 6.12 (ddd, *J* = 2.4, 3.8, 10.7 Hz, 1H), 5.87 (dm, *J* = 10.7 Hz, 1H), 4.71 (d, *J* = 7.0 Hz, 1H), 3.74 (ddd, *J* = 2.6, 4.8, 7.8 Hz, 1H), 3.26-3.22 (m, 1H), 2.80 (dt, *J* = 3.1, 8.0 Hz, 1H), 2.43 (s, 6H), 1.80-1.40 (m, 2H), 1.51 (s, 9H), 0.98 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.4, 135.4, 116.6, 73.9, 61.2, 58.8, 57.5, 54.6, 43.1, 28.4, 26.7, 10.4; IR (neat film) ν_{max} = 3271, 3033, 2968, 2940, 2868, 2818, 2777, 2240, 1952, 1884, 1814, 1737, 1650, 1604, 1585, 1519, 1455, 1392, 1364, 1311, 1025 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{15}H_{27}N_3O_3S$: 329.1773; found: 329.1765 $[M]^+$

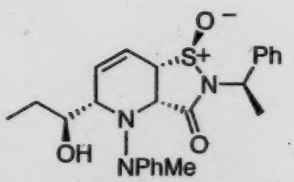
(*1R,3aR,5R,7aR*)-1-Dimethylamino-5-[(*S*)-hydroxypropyl]-6-(*R*-methylbenyl)-3a,4,5,7a-tetrahydroisothiazolo[3,4-b]pyridin-3-(2H)one-1-oxide (48g)



TLC (70% EtOAc/Hexane, $KMnO_4$): 0.25; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.28-7.24 (m, 5H), 6.05 (ddd, *J* = 2.3, 3.9, 10.8 Hz, 1H), 5.77 (dm, *J* = 10.9 Hz, 1H), 5.45 (q, *J* = 7.1 Hz, 1H), 4.81 (d, *J* = 3.8 Hz, 1H), 3.80 (dq, *J* = 2.5, 8.5 Hz, 1H), 3.67 (bs, 1H), 3.22-

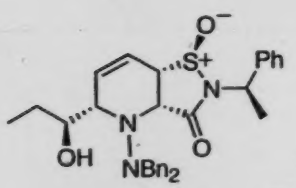
3.18 (m, 1H), 2.55 (dt, *J* = 2.7, 8.2 Hz, 1H), 2.45 (s, 6H), 1.80 (d, *J* = 7.2 Hz, 3H), 1.57-1.32 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.8, 139.6, 135.2, 128.6, 128.2, 126.6, 127.2, 116.4, 73.4, 60.7, 58.9, 54.3, 54.0, 43.2, 26.6, 19.6, 10.3; IR (CH_2Cl_2 cast) ν_{max} = 3493, 3031, 2978, 2938, 2875, 2817, 2776, 1708, 1496, 1454, 1398, 1380, 1267, 1101 cm^{-1}; HRMS (ES): *m/z*: calcd for $C_{19}H_{27}N_3O_3SNa$: 400.1671; found: 400.1672 $[M+Na]^+$; $[\alpha]_D^{23}$ = -19.95 (c = 2.2 in $CHCl_3$).

Rac-(*1R,3aR,5R,7aR*)-1-(methylphenylamino)-5-[(*S*)-hydroxypropyl]-6-(*R*-methylbenzyl)-3a,4,5,7a-tetrahydroisothiazolo[3,4-b]pyridin-3-(2H)one-1-oxide (48h)



TLC (30% EtOAc/Hexane, $KMnO_4$): 0.12; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36-7.22 (m, 9H), 6.88 (dd, *J* = 7.1, 7.2 Hz, 1H), 6.15 (ddd, *J* = 2.5, 3.4, 10.8 Hz, 1H), 5.86 (dm, *J* = 10.8 Hz, 1H), 5.48 (q, *J* = 7.2 Hz, 1H), 4.67 (d, *J* = 6.6 Hz, 1H), 3.87-3.82 (m, 1H), 3.46 (dt, *J* = 3.0, 6.2 Hz, 1H), 3.37 (d, *J* = 5.8 Hz, 1H), 3.0 (s, 6H), 2.95-2.91 (m, 1H), 1.80 (d, *J* = 7.3 Hz, 3H), 1.56-1.42 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.0, 148.8, 139.6, 135.9, 129.6, 128.9, 128.5, 127.4, 120.0, 117.0, 114.2, 75.0, 64.7, 59.2, 57.4, 54.3, 36.2, 27.2, 19.9, 10.7; IR (CH_2Cl_2 cast) ν_{max} = 3515, 3032, 2964, 2876, 1704, 1598, 1497, 1453, 1381, 1318, 1270, 1105 cm^{-1}; HRMS (ES): *m/z*: calcd for $C_{24}H_{29}N_3O_3S$: 439.19; found: 462.1819 $[M+Na]^+$

Rac-(*1R,3aR,5R,7aR*)-1-Dibenzyl-5-[(*S*)-hydroxypropyl]-6-(*R*-methylbenzyl)-3a,4,5,7a-tetrahydroisothiazolo[3,4-b]pyridin-3-(2H)one-1-oxide (48i)



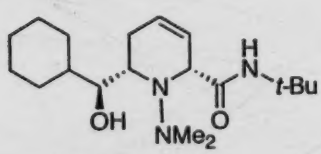
TLC (30% EtOAc/hexane, $KMnO_4$): 0.3; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.38-7.10 (m, 15H), 6.06 (dm, *J* = 10.4 Hz, 1H), 5.76 (d, *J* = 10.6 Hz, 1H), 5.38 (q, *J* = 7.2 Hz, 1H), 4.97 (d, *J* = 6.9 Hz, 1H), 3.79 (d, *J* = 13.8 Hz, 2H), 3.73 (d, *J* = 13.4 Hz, 2H), 3.62-3.53 (m, 1H), 3.35-3.28 (m, 1H), 3.13 (bs, 1H), 2.41-2.31 (m, 1H), 1.77 (d, *J* = 7.2 Hz, 3H), 1.39-1.16 (m, 2H), 0.80 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.75, 139.9, 138.1, 134.9, 128.9, 128.5, 128.3, 128.0, 127.4, 126.9, 117.1, 73.43, 60.7, 58.5, 57.8, 57.4, 53.9, 26.1, 20.0, 10.2; IR ($CHCl_3$ cast) ν_{max} = 3500, 3062, 3030, 2977, 2933, 2876, 2840, 1712, 1606, 1585, 1495, 1454, 1397, 1378, 1306, 1290, 1205, 1161, 1133, 1100, 1028, 974, 938, 898, 842, 749, 733, 698, 628, 587, 550, 521, 467 cm^{-1}; HRMS (ES): *m/z*: calcd for $C_{31}H_{35}N_3O_3SNa$: 552.2297; found: 552.2296 $[M+Na]^+$; Elemental Analysis calcd (%) for $C_{31}H_{35}N_3O_3S$ (529): C 70.32, H 6.62, N 7.93, S 6.04; found: C 70.20, H 6.57, N 7.86, S 6.04.

4.6.6 Retro-sulfinyl-ene reaction: typical procedure

Compound **47e** (0.91 g, 2.5 mmol) was dissolved in 10 mL of acetone at 0° C. Cold aqueous 5% NaOH solution (20 mL) was added and the reaction mixture was stirred for 30 min, then brought to room temperature and stirred for 6 h. The solution was cooled again on ice and 10% aqueous HCl was added over 20 min (final pH ~ 1). Stirring was

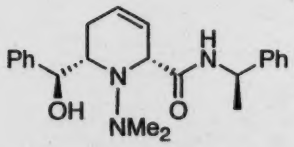
continued for an additional 30 min, then 5% $NaHCO_3$ was added slowly until pH 6.0-6.5. The solvent was evaporated to dryness and $CHCl_3$ (60 mL) was added to the resulting solid. The suspension was stirred for 5 min prior to the addition of $MgSO_4$. All solid particles were removed by filtration and the filtrate was refluxed for 16 h. The reaction mixture was then cooled to room temperature and the solvent was removed under reduced pressure. The resulting colorless oil was purified by flash chromatography using 25% ethyl acetate in hexane to afford a pale yellow solid in 69 % yield.

Rac-(2*R*,6*S*)-1-Dimethylamino-6-[(*S*)-hydroxycyclohexylmethyl]-1,2,5,6-tetrahydropyridine-2-carboxylic acid-*tert*-butylamide (50a)



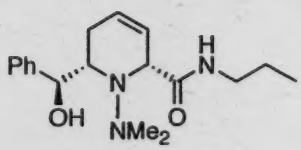
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32 (bs, 1H), 6.69 (bs, 1H), 6.04-6.00 (m, 1H), 5.91-5.87 (m, 1H), 3.93 (d, *J* = 5.4 Hz, 1H), 3.45 (dd, *J* = 1.9, 7.4 Hz, 1H), 2.86-2.78 (m, 1H), 2.40 (s, 6H), 2.18-2.12 (m, 1H), 1.82-1.76 (m, 3H), 1.68-1.44 (m, 4H), 1.42-1.20 (m, 4H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 126.6, 125.7, 81.8, 56.5, 55.7, 54.9, 50.7, 40.1, 39.9, 30.5, 29.4, 28.6, 26.9, 26.8, 26.5, 26.4, 26.3, 26.2, 25.3, 24.8, 24.6; IR (CH_2Cl_2 cast) ν_{max} = 3263, 3043, 2926, 2851, 2812, 2771, 1649, 1532, 1453, 1363 cm^{-1}; HRMS (ES): *m/z*: calcd for: $C_{19}H_{35}N_3O_2$: 337.27; found: 338.3 $[M+H]^+$

Rac-(2*R*,6*S*)-1-Dimethylamino-6-[(*R*)-hydroxybenzyl]-1,2,5,6-tetrahydropyridine-2-carboxylic acid-[(*R*)-methylbenzyl)amide (50b)



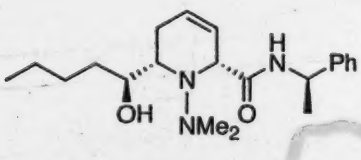
TLC (EtOAc, $KMnO_4$): 0.5; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 8.4 Hz, 1H), 7.40-7.26 (m, 10H), 6.22 (ddd, *J* = 2.0, 5.1, 9.6 Hz, 1H), 5.82-5.74 (m, 1H), 5.10 (app p, *J* = 7.0 Hz, 8.2, 1H), 4.61 (d, *J* = 8.2 Hz, 1H), 4.11, (m, 1H), 3.04 (dt, *J* = 5.3, 8.7 Hz, 1H), 2.42 (s, 6H), 1.74-1.62 (m, 2H), 1.50 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 142.8, 141.8, 128.6, 128.4, 128.0, 127.4, 127.3, 126.15, 126.07, 126.05, 125.0, 80.7, 59.2, 56.7, 48.7, 40.4, 26.4, 26.0, 21.8, 17.8; IR (neat) ν_{max} = 3270, 3085, 3062, 3031, 2974, 2939, 2816, 2775, 2241, 1950, 1883, 1809, 1737, 1651, 1604, 1585, 1520, 1495, 1455, 1377 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{23}H_{29}N_3O_2$: 379.2260; found: 379.2254 $[M]^+$

Rac-(2*R*,6*S*)-1-Dimethylamino-6-[(*R*)-hydroxybenzyl]-1,2,5,6-tetrahydropyridine-2-carboxylic acid-*n*-propylamide (50c)



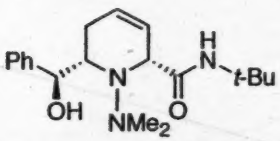
TLC (EtOAc, $KMnO_4$): 0.19; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.42-7.22 (m, 5H), 6.89 (bs, 1H), 5.96 (ddd, *J* = 2.7, 5.2, 9.5 Hz, 1H), 5.73-5.68 (m, 1H), 4.60 (d, *J* = 8.2 Hz, 1H), 4.10 (d, *J* = 4.7 Hz, 1H), 3.21 (q, *J* = 7.0 Hz, 2H), 3.00-2.93 (m, 1H), 2.50 (s, 6H), 1.68-1.48 (m, 4H), 0.93 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 142.0, 128.4, 128.0, 127.4, 126.1, 126.05, 81.3, 59.2, 56.6, 41.0, 40.2, 26.2, 22.9, 11.5; HRMS (EI): *m/z*: calcd for $C_{18}H_{27}N_3O_2Na$: 340.1996; found: 340.1994 $[M]^+$

Rac-(*2R,6S*)-1-Dimethylamino-6-[(*S*)-hydroxypentyl]-1,2,5,6-tetrahydropyridine-2-carboxylic acid-[(*R*)-methylbenzyl)amide (50d)



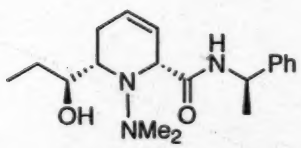
TLC (EtOAc, $KMnO_4$): 0.2; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 8.4 Hz, 1H), 7.36-7.24 (m, 5H), 6.42 (bs, 1H), 6.05 (ddd, *J* = 2.8, 5.3, 9.1 Hz, 1H), 5.98-5.90 (m, 1H), 5.08 (app p, *J* = 7.0 Hz, 1H), 4.04 (d, *J* = 5.1 Hz, 1H), 3.62 (dt, *J* = 2.2, 8.0 Hz, 1H), 2.71 (ddd, *J* = 4.3, 7.7, 11.7 Hz, 1H), 2.31 (s, 6H), 2.23-2.17 (m, 1H), 1.85-1.77 (m, 1H), 1.55-1.31 (m, 7H), 1.47 (d, *J* = 6.9 Hz, 3H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.9, 143.0, 128.8, 127.5, 126.2, 126.1, 77.51, 58.4, 56.2, 48.6, 40.0, 33.7, 27.1, 25.7, 23.0, 21.9, 14.1; IR (CH_2Cl_2 cast) ν_{max} = 3338, 3042, 2938, 2816, 2776, 1952, 1621, 1531, 1455, 1381, 1265 cm^{-1}; HRMS (ES): *m/z*: calcd for: $C_{21}H_{33}N_3O_2$: 359.26; found: 360.26 $[M+H]^+$

Rac-(*2R,6S*)-1-Dimethylamino-6-[(*R*)-hydroxybenzyl]-1,2,5,6-tetrahydropyridine-2-carboxylic acid-*tert*-butylamide (50e)



TLC (50% EtOAc/hexane, $KMnO_4$): 0.16; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.27-7.39 (m, 5H), 5.93 (ddd, *J* = 2.7, 5.1, 9.4 Hz, 1H), 5.65-5.70 (m, 1H), 4.56 (d, *J* = 8.2 Hz, 1H), 3.97 (dm, *J* = 5.1 Hz, 1H), 2.93 (ddd, *J* = 4.3, 8.2, 12.8 Hz, 1H), 2.52 (s, 6H), 1.58-1.66 (m, 1H), 1.44-1.54 (m, 1H), 1.34 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.0, 142.0, 128.4, 128.0, 127.4, 126.3, 125.8, 81.8, 59.2, 57.3, 50.8, 40.2, 28.7, 26.4; IR (CH_2Cl_2 cast) ν_{max} = 3456, 3037, 2973, 2938, 2874, 2816, 2775, 1707, 1456, 1397cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{19}H_{30}N_3O_2$: 332.2333; found: 332.2332 $[M]^+$.

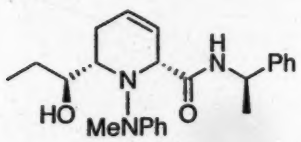
(*2R,6S*)-1-Dimethylamino-6-[(*S*)-hydroxypropyl]-1,2,5,6-tetrahydropyridine-2-carboxylic acid-[(*R*)-methylbenzyl]amide (50g)



TLC (80% EtOAc/ Hexane, $KMnO_4$): 0.13; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 8.1 Hz, 1H), 7.36-7.20 (m, 5H), 6.42 (bs, 1H), 6.04-5.98 (m, 1H), 5.94-5.82 (m, 1H), 5.04 (q, *J* = 6.9 Hz, 1H), 4.02 (d, *J* = 8.8 Hz, 1H), 3.53 (dt, *J* = 3.0, 8.1 Hz, 1H), 2.74-264 (m, 1H), 2.27 (s, 6H), 2.15 (ddd, *J* = 4.6, 6.6, 16.5 Hz, 1H), 1.84-1.72 (m, 1H), 1.66-1.52 (m, 1H), 1.43 (d, *J* = 6.9 Hz, 3H), 1.42-1.26 (m, 1H), 0.97 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.9, 142.9, 128.7, 127.5, 126.4, 126.2, 126.1, 78.6, 58.1, 56.1, 48.6,

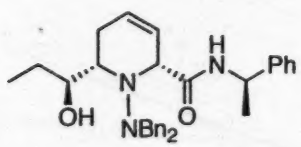
39.8, 26.7, 25.6, 21.8, 9.3; IR ($CHCl_3$ cast) ν_{max} = 3249, 3040, 2972, 2937, 2872, 2823, 2772, 1645, 1584, 1530, 1495, 1453, 1375, 1323 cm^{-1};HR MS (ES): *m/z*: calcd for $C_{19}H_{30}N_3O_2$: 332.2333; found: 354.2157 [M+Na]+; $[\alpha]_D^{23}$ = +121.3 (c = 2.0 in $CHCl_3$)

Rac-(2*R*,6*S*)-(1-Methylphenylamino)-6-[(*S*)-hydroxypropyl]-1,2,5,6-tetrahydropyridine-2-carboxylic acid-[(*R*)-methylbenzyl)amide (50h)



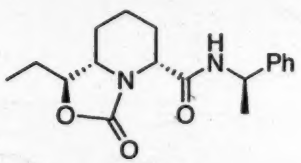
TLC (50% EtOAc/ hexane, $KMnO_4$): 0.13; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.55-7.42 (bs, 1H), 7.23-7.18 (m, 3H), 7.15-7.03 (m, 4H), 6.93-6.88 (d, *J* = 7.3 Hz, 2H), 6.72 (app t, *J* = 1.2, 7.2 Hz, 1H), 6.01-5.90 (m, 2H), 4.88 (app p, *J* = 7.2 Hz, 1H), 4.10-4.07 (m, 1H), 3.52-3.43 (bs, 1H), 3.05 (dt, *J* = 6.0, 7.2 Hz, 1H), 2.90 (s, 3H), 2.62-2.56 (bs, 1H), 2.27-2.22 (m, 2H), 1.70-1.54 (m, 1H), 1.36 (d, *J* = 7.2 Hz, 3H), 1.36-1.28 (m, 1H), 0.86 (t, *J* = 8.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.0. 149.5, 143.1, 129.1, 128.5, 128.4, 127.1, 126.4, 125.9, 118.8, 113.7, 74.3, 64.0, 61.1, 49.2, 32.8, 27.0, 26.2, 24.8, 21.7, 10.1; HRMS (EI): *m/z*: calcd for $C_{24}H_{31}N_3O_2$: 393.2416; found: 393.2404 $[M]^+$

(2*R*,6*S*)-1-Dibenzylamino-6-[(*S*)-hydroxypropyl]-1,2,5,6-tetrahydropyridine-2-carboxylic acid-[(*R*)-methylbenzyl)amide (50i)



TLC (30% EtOAc/ hexane, $KMnO_4$): 0.22; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.48-7.08 (m, 15H), 6.31 (dm, *J* = 12.5 Hz, 1H), 5.93 (dm, *J* = 13.1 Hz, 1H), 5.07 (app p, *J* = 7.1 Hz, 1H), 4.35-4.31 (m, 1H), 3.90-3.52 (m, 4H), 3.28-3.10 (m, 2H), 2.41 (m, 1H) 2.03 (m, 1H), 1.63 (d, *J* = 4.7 Hz, 1H), 1.49 (m, 1H), 1.30-1.21 (m, 1H), 1.25 (d, *J* = 8.2 Hz, 3H), 0.87 (t, *J* = 7.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.7, 143.2, 138.8, 128.8, 128.6, 128.5, 127.4, 127.2, 126.8, 126.6, 124.6, 71.8, 62.1, 58.0, 57.5, 48.4, 26.5, 22.8, 20.3, 8.9; IR ($CHCl_3$ cast) ν_{max} = 3282, 3085, 3062, 3029, 2971, 2930, 2875, 1644, 1603, 1585, 1495, 1453, 1376, 1325, 1216, 1104, 1073, 1028, 974, 912, 836, 750, 698. 547 cm^{-1}; HRMS (ES): *m/z*: calcd for $C_{31}H_{35}N_3O_2Na$: 506.2784; found: 506.2784 $[M+Na]^+$; $[\alpha]_D^{23}$ = +44.7 (c = 2.3 in $CHCl_3$)

4.6.7 (*1S,5R,8aS*)-1-Ethyl-hexahydro-3-oxo-4H-oxazolo[3,4-a]-5-carboxylic acid [(*R*)-methylbenzyl)amide] (51)



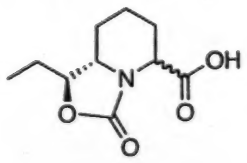
Compound **49i** (1.1 g, 2.3 mmol) was dissolved 10-12 ml of ethanol, 1-2 mL of a slurry suspension of Raney nickel in water (grade 2800, Aldrich) was added and the mixture was shaken at 60° C under 450 psi of hydrogen atmosphere for 24 to 48 h. The reaction mixture was then removed from the hydrogenation bomb and filtered on Celite. The solvent was removed and the mixture was dissolved in CH_2Cl_2. The crude product was obtained by acid-base extraction and was carried through the next step without further purification.

The crude product was dissolved in CH_2Cl_2 and carbonyl diimidazole (4 equiv) was added. The mixture was stirred at RT overnight, after which it was washed with 10%

aqueous HCl, then with brine. The organic layer was dried over magnesium sulfate, filtered and the solvent was removed to afford a white solid which was recrystallized was ethyl acetate/hexane to afford the product in 85 to 95% yield.

^{1}H NMR (500MHz, $CDCl_3$): δ = 7.35-7.18 (m, 5H), 6.14 (d, *J* = 7.2 Hz, 1H), 5.16 (q, *J* = 7.0 Hz, 1H), 4.12 (dt, *J* = 6.3, 9.2 Hz, 1H), 3.54 (dd, *J* = 3.7, 9.2 Hz, 1H), 3.18-3.12 (m, 1H), 1.96-1.62 (m, 6H), 1.52 (d, *J* = 6.9 Hz, 3H), 1.46-1.37 (m, 2H), 1.02 (t, *J* = 7.51 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.0, 157.8, 142,8, 128.6, 127.3, 126.4, 82,7, 61.0, 57.8, 49.0, 28.9, 27.4, 25.6, 9.54; IR ($CHCl_3$ cast) ν = 3285, 3063, 3029, 2967, 2859, 1760, 1656, 1604, 1549, 1495, 1447, 1417, 139575, 1346, 1310, 1259, 1218, 1185, 1154, 1135, 1082, 1059, 1042, 1019 cm^{-1}; HRMS (ES): *m/z*: calcd for $C_{18}H_{24}N_2O_3$: 316.1787; found: 316.1782 $[M]^+$; elemental analysis calcd (%) for $C_{18}H_{24}N_2O_3$ (316): C 68.35, H 7.59, N 8.86; found: C 68.13, H 8.04, N 8.82; $[\alpha]_D^{23}$ = +76.4 (c = 0.33 in $CHCl_3$)

4.6.8 9-(*1S,5epi,8aS*)-1-Ethyl-hexahydro-3-oxo-4H-oxazolo[3,4-a]-5-carboxylic (50 to 52)

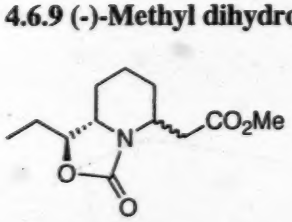


Compound **50** (0.21 g, 0.66 mmol) was dissolved in 6 mL of $AcOH/Ac_2O$ and cooled at 0° C. Sodium nitrite (0.45 g, 6.60 mmol) was added and the mixture was stirred on ice for 30 min at RT for 3 h after which, it was diluted with ethyl acetate, washed with water (2 × 10 mL), 5% sodium bicarbonate and brine. The organic layer was dried over $MgSO_4$ and the solvent was evaporated to afford a colorless oil, which was dissolved in 4 ml of THF on ice. 2 mL of 0.6 M aqueous LiOH was added, and the reaction was slowly

warmed up to RT overnight. After 16 h, the mixture was cooled on ice, diluted with ethyl acetate and water, carefully acidified (pH = 1) and transferred to a separatory funnel. The two layers were separated and the aqueous layer was returned to the funnel and extracted with ethyl acetate. The desired carboxylic acid was recovered by extraction of the combined organic layer with 5% aqueous $NaHCO_3$ solution (3-10 mL), treatment with 10% aqueous HCl on ice and extraction again with ethyl acetate. The combined organic layers were dried over magnesium sulfate and the solvent was removed to afford 0.11 g of an oily residue as a mixture of epimers (79%) in 2:1 ratio.

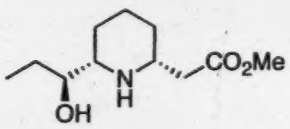
^{1}H NMR (300MHz, $CDCl_3$): δ = 7.21 (bs, 2H), 4.65 (d, *J*= 5.5 Hz, 1H, epimer A), 4.14-4.0 (m, 2.3H, epimer A + B), 3.79 (dd, *J* = 3.5, 10.4 Hz, 1.3H, epimer B), 3.63 (ddd, *J* = 3.3, 7.6 and 11.2Hz, 0.85 H, epimer A), 3.20 (ddd, *J* = 1.7, 9.1 and 12.1 Hz, 1.6H, epimer B), 2.22 (d, J = 7.3Hz, 1H, A or B), 2.08-1.94 (m, 3H, A and B), 1.92-1.66 (m, 9H, A and B), 1.54-1.20 (m, 8H, A and B), 1.0 (m, 7H, A and B); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.0, 174.0, 157.2, 157.1, 83.2, 83.0, 60.3, 57.0, 55.7, 51.9, 29.7, 29.6, 27.5, 26.6, 26.0, 25.6, 21.2, 19.6, 9.4, 8.9. IR ($CHCl_3$ cast) ν = 2940, 2252, 1748, 1530, 1430, 1396, 1340, 1310, 122, 1239, 1188, 1080.

4.6.9 (-)-Methyl dihydropalustramate (51 to 52)



Compound **51** (220 mg, 1.02 mmol) was dissolved in dichloromethane (4 mL) and the solution was cooled on ice. DMF (5 μl) was added, followed by oxalyl chloride (0.13 mL, 1.34 mmol) and the mixture was stirred for 15 min, then brought to RT and stirred for 4

h. The solvent was removed and the residue was dissolved in 2 mL of THF and added to an ice-cold solution of CH_2N_2 in ether (freshly prepared, 8-10 mmol). After 30 min, the reaction mixture was brought to RT and stirred for 16 h. The solvent was removed to afford a pale yellow oil, which was dissolved in 10 mL of methanol. The solution was cooled to 0° C, 50 mg solution of silver benzoate and 0.3 mL of freshly distilled triethylamine were sequentially added, and the resulting mixture was stirred at RT for 27 h in the exclusion of light. The reaction mixture was filtered through Celite, the solvent was removed under reduced pressure and the two diastereomers were separated by flash chromatography using 20% ethyl acetate/hexane in 59% yield. (Note: both compound were contaminated by small amount of other impurities



Compound **52** (70 mg, 0.3 mmol) was disolved in a 1:1 mixture of dimethoxyethane/water (8.0 ml), then barium hydroxide (0.37 g, 2.0 mmol) was added and the reaction mixture was refluxed for 48 h. The solution was then cooled to RT and carbon dioxode was bubbled through for 3-5 min. The white precipates were removed by filtration and the solvent was evaporated to afford a white solid, which was dissolved in 30 mL of anhydrous methanol. 20-25 drops of thionyl chloride was carefully added and the reaction mixture was refluxed overnight then cooled to rt. Methanol was removed and the residue was dissolved in dichloromethane and washed with aqueous sodium bicarbonate and brine. The solvent was removed under reduced pressure to afford a black oil, which was purified by flash chromatography using 4% MeOH/CH_2Cl_2 to afford 39 mg (62%) of the product, (-)-methyl dihydropalustramate (**3**).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.65 (s, 3H), 3.32-3.28 (m, 1H), 3.26-3.05 (bs, 2H) 3.02-2.95 (m, 1H), 2.56-2.42 (m, 1H), 2.43 (d, *J* = 6.7 Hz, 2H), 1.90-1.84 (m, 1H), 1.68-1.52 (m, 3H), 1.49-1.35 (m, 2H), 1.22-1.06 (m, 2H), 0.98 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.6, 75.2, 60.8, 53.3, 51.5, 40.8, 31.6, 27.9, 26.5, 23.9, 9.7; HRMS (ES): *m/z*: calcd for $C_{11}H_{22}NO_3$: 216.1594; found: 216.1593 $[M+H]^+$; $[\alpha]_D^{23}$ = -26 (c = 1.35 in CH_3OH); litt. $[\alpha]_D^{23}$ = -23 (c = 0.8 in CH_3OH)[5,13,31]

4.7 References

(1) For a recent review on the synthesis of substituted piperidines, see: Weintraub, P.M.; Sabol, J.S.; Kane, J.A.; Borcherding, D.R. *Tetrahedron* **2003**, *59*, 2953-2989.

(2) Karrer, P.; Eugster, C.H. *Helv. Chim. Acta* **1948**, *31*, 1062-1066.

(3) Eugster, C.H. *Heterocycles* **1976**, *4*, 51-105.

(4) Turner, R. B.; Woodward, R. B. The Chemistry of the Cinchona Alkaloids. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1953; Vol. 3, Chapter 16.

(5) Mayer, C.; Green, C.L.; Trueb, W.; Wälchli, P.C.; Eugster, C.H. *Helv. Chim. Acta* **1978**, *61*, 905-921.

(6) Wasserman, H. H.; Leadbetter, M. R.; Kopka, I. E. *Tetrahedron Lett.* **1984**, 2391-2394

(7) Raheem, I. T.; Goodman S. N.; Jacobsen E. *J. Am . Chem. Soc.* **2004**, *126*, 706-707.

(8) Ogawa, M.; Yoda, I.; Natsume M. *Heterocycles* **1984**, *21*, 403-404.

(9) Natsume M.; Ogawa, M. *Chem. Pharm. Bull.* **1982**, *30*, 3442-3445.

(10) Natsume M.; Ogawa, M. *Chem. Pharm. Bull.* **1982**, *30*, 3442-3445.

(11) Hirai, Y.; Watanabe, J.; Nozaki, T.; Yokoyama, H.; Yamaguchi, S. *J. Org. Chem.* **1997**, *62*, 776-777.

(12) Angle, S. R.; Henry, R. M. *J. Org. Chem.* **1998**, *63*, 7490-7497.

(13) Muraoka, O.; Zheng, B.-Z.; Okumura, K.; Tanabe, G.; Momose, T.; Eugster, C. H. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1567-1575.

(14) Stork, G.; Niu, D.; Fujimoto, A.; Koft, E. R.; Balkovec, J. M.; Tata, J. R.; Dake, G. *J. Am. Chem. Soc.* **2001**, *123*, 3239-3242.

(15) Kuethe, J. T.; Comins, D. L. *Org. Lett.* **2000**, *2*, 855-857.

(16) Tailor, J.; Hall, D. G. *Org. Lett.* **2000**, *2*, 3715-3718.

(17) Touré, B. B.; Hoveyda, H. R.; Tailor, J.; Ulaczyk-Lesanko, A.; Hall, D .G. *Chem. Eur. J.* **2003**, *9*, 466-474.

(18) Weiler, E. D.; Brennan, J. J. *J. Heterocyl. Chem.* **1978**, *15*, 1299-1302.

(19) Wichterle, O.; Rocek, J. *Chem. Listy* **1953**, *47*, 1768-1780. Wichterle, O.; Rocek, J. *Coll. Czechoslov. Chem. Commun.* **1954**, *19*, 282.

(20) Kresze, G.; Wucherpfennig, W. *Angew. Chem. Int. Ed.* **1967**, *6*, 49.

(21) Mock, W. L.; Nugent, R. M. *J. Org. Chem.* **1978**, *43*, 3433-3434.

(22) Garigipati, R. S.; Morton, J. A.; Weinreb, S. M. *Tetrahedron Lett.* **1983**, *24*, 987-990.

(23) Rogic, M. M.; Masilamani, D. *J. Am. Chem. Soc.* **1977**, *99*, 5219-5220.

(24) Waldner, A. *Tetrahedron Lett.* **1989**, *30*, 3061-3064.

(25) For example, N-acylated *cis*-2,6-disubstituted piperidines exist in the "diaxial" conformation to escape $A^{1,3}$ strain between the planar exocyclic amide group and the neighboring substituents in the "diequatorial" conformation: Natsume, M.; Ogawa, M. *Chem. Pharm. Bull.* **1982**, *30*, 3442-3445, and references cited. In the case of compounds **48**, the planar hydrazine can be considered isosteric to an acyl group.

(26) White, E. M. *J. Am. Chem. Soc.* **1955**, *48*, 2424-2426.

(27) Evans, D. A.; Carter, P. H.; Dinsmore, C. J.; Barrow, J. C.; Katz, J. L.; Kung, D. W. *Tetrahedron Lett.* **1997**, *38*, 4535-4538.

(28) Bailey, T.R.; Garigipati, R.S.; Morton, J.A.; Weinreb, S.M. *J. Am. Chem. Soc.* **1984**, *106*, 3240-3245.

(29) Overberger, G. H. *J. Am. Chem. Soc.* **1955**, 4100-4104.

(30) Lewis, S. N.; Miller, G. A.; Hausman, M.; Szamborki, E. C. *J. Heterocycl. Chem.* **1971**, *8*, 571-586.

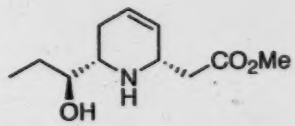
(31) The ^{1}H NMR and the ^{13}C spectrum were obtained from Prof. Muraoka, Osaka University, Japan.

Chapter 5

Design of a Non-Reductive Method for Chemoselective Cleavage of Hydrazines in the Presence of Unsaturations. Application to a Stereoconvergent Three-Component Synthesis of (-)-Methyl Palustramate

5.1 Introduction

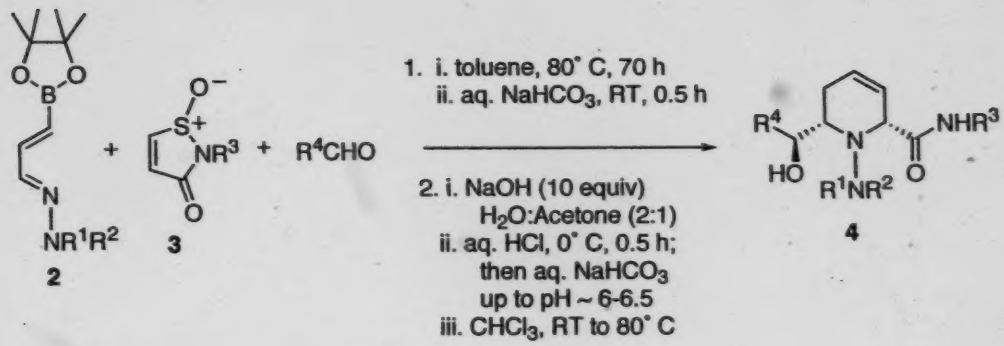
The next major advance in this project was the development of a chemoselective hydrazine cleavage method and its application to the synthesis of (-)-methyl palustramate (**1**), a palustrine family member possessing a C3-C4 unsaturation (Figure 5.1).



1

Figure 5.1. (-)-methyl palustramate

Our sequential tandem aza[4+2]cycloaddition/allylboration/retro-sulfinyl-ene reaction, discussed in Chapter 4, allowed the efficient construction of the entire core **4** including all the requisite stereocenters and the C3-C4 double bond of target **1** in only two synthetic operations (Scheme 5.1).



Scheme 5.1. Sequential tandem aza[4+2]cycloaddition/allylboration/retro-sulfinyl-ene approach to palustrine alkaloids

At this stage, the completion of the synthesis of **1** now relies only upon a successful one-carbon homologation of the carboxamide side chain, and the chemoselective cleavage of a tetraalkylhydrazine in the presence of the C3-C4 double bond (Figure 5.2).

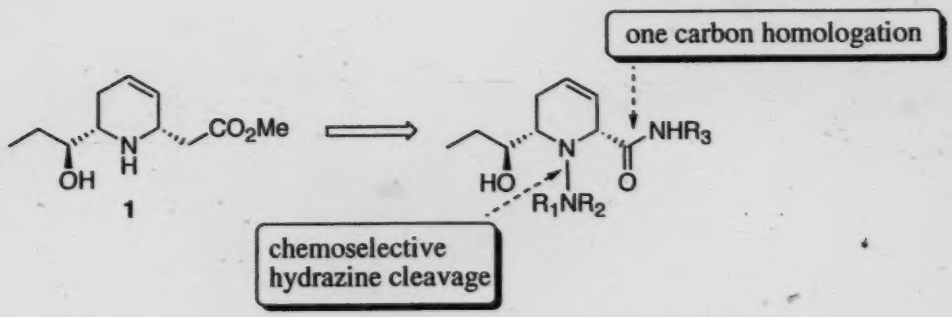
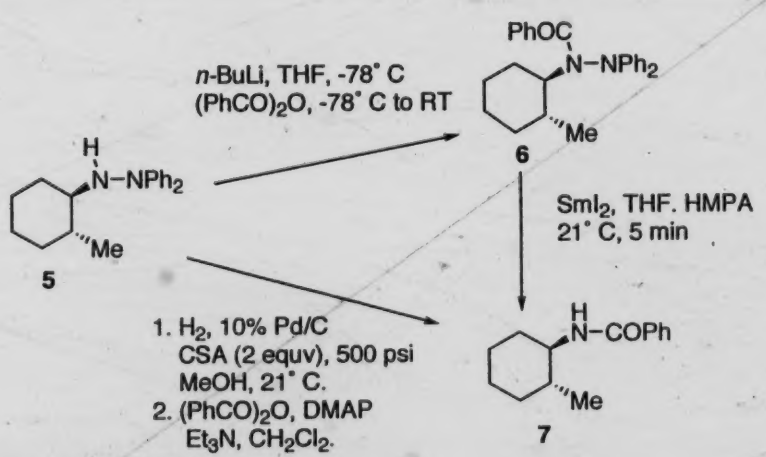


Figure 5.2. Proposed retrosynthesis of (-)-methyl palustramate (**1**).

However, prior to this work, the cleavage of a tetraalkylhydrazine moiety in the presence of double or triple bonds was virtually unknown. Current methodologies for the cleavage of alkylhydrazines involve hydrogenolysis under high hydrogen pressure conditions with Pd/C,[1,2] $Pd(OH)_2$,[3] PtO_2,[4,5] Pt,[6] or Raney nickel[7,8,9]. Likewise, hydroboration has also been used for the cleavage of alkylhydrazines.[10,11] None of the above methods, however, are compatible with alkenes and alkynes.



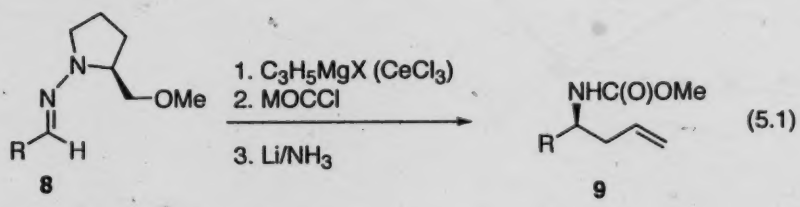
Scheme 5.2. Hydrazine activation strategy towards reductive cleavage

An indirect preactivation strategy has also been employed for the cleavage of alkylhydrazines. For instance, compound **5** was efficiently converted into amide **7** via a butyl lithium mediated deprotonation of the hydrazine and acylation sequence followed by treatment with samarium diiodide (SmI_2). Amide **7** was also conveniently prepared by a hydrogenolysis of the hydrazine using 10% Pd/C followed by acylation (Scheme 5.2).[12]

For unsaturated molecules, a three-step chemoselective hydrazine cleavage procedure may be employed. This sequence consists of first activating the hydrazine as

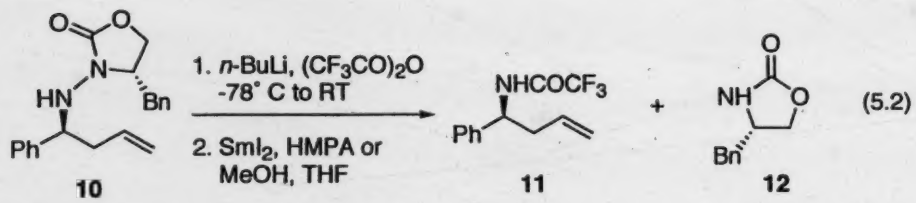
its acyl or carbamoyl derivative, followed by treatment with sodium or lithium[13,14,15] in liquid ammonia or SmI_2,[16,17] and final deprotection to liberate the free amine. Unfortunately, as illustrated above in Scheme 5.2, and also in Equation 5.2 (see next page), the acylation of hydrazines requires the use of very basic alkyllithium species incompatible with epimerization-prone or other base-sensitive substrates. In addition, alkene isomerization, and in some cases reduction of conjugated polyenes, may compete.

Alternatively, products resulting from the addition of organometallic reagents to imines can be acylated *in situ* by simple addition of the appropriate reagent (Equation 5.1). Regardless of the activation method employed, the hydrazine cleavage typically delivers secondary amides, a dreaded class of intermediate in organic synthesis, as these compounds are notoriously difficult to hydrolyse. To obtain the corresponding amine, the use of harsh reaction conditions incompatible with sensitive functionalities cannot be avoided.



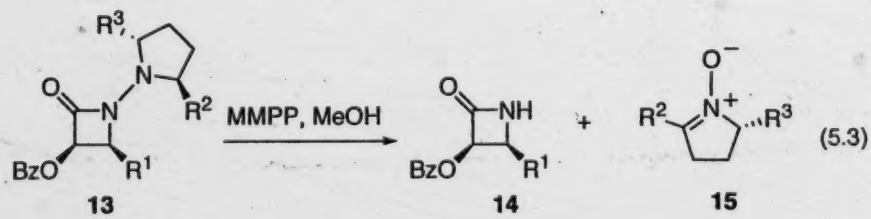
8 **9** (5.1)

The use of a trifluoroacetyl activating group was recently advocated by Friestad and coworkers.[18] For instance, hydrazide **10** was first acylated with trifluoroacetyl anhydride followed by treatment with SmI_2 to afford protected amthe ine **11**. While the trifluoroacetyl protecting group can be removed under mild reaction conditions, it is still plagued by the other drawbacks mentioned above: namely the activating group still needs to be installed often under harsh reaction conditions, and then removed (Equation 5.2).



(5.2)

Finally, organic peroxides such as magnesium monoperoxyphtalate (MMPP) have also been used for the cleavage of activated hydrazines.[12,19,20] As illustrated in Equation 5.3, hydrazides **13** can be selectively oxidized, with the resulting *N*-oxide undergoing an N-N fragmentation process triggered by the abstraction of the α-hydrogen. This method, however, is plagued by regioselective *N*-acylation issues. Furthermore, this method has not yet been applied to substrates possessing any unsaturation.



(5.3)

In summary, a mild and general method for the chemoselective cleavage method hydrazines has remained elusive so far. The strategies described above, although they preserve non-conjugated double bonds during the hydrazine cleavage operation, do suffer lengthy functional group manipulations. For instance, the installation and subsequent removal of an activating group is required. Furthermore, they are not applicable to unsymmetrical tetraalkylhydrazines like those employed in our studies.

Interestingly, our approach to target **1** unveiled an important methodological gap in organic synthesis. In light of the synthetic usefulness of hydrazines,[21] which are employed in a wide variety of C-C and C-N bond forming processes, we next sought to address this important issue.

5.2 Results and Discussion

5.2.1 Model Studies towards (-)-methyl palustramate (1)

5.2.1.1 Examination of traditional methods for hydrazine cleavage.

Our synthetic plan, from the outset, first stressed the need to cleave the N-N bond in a chemoselective manner that would preserve the C3-C4 double bond. We envisioned three main strategies to accomplish this task:

1. The use of hydrazides or *N*-alkoxyamines, which can usually be cleaved under milder reaction conditions to afford the desired amines (Figure 5.3).
2. Activation of trialkylhydrazines after the retro-ene reaction step.
3. Explore the feasibility of a direct cleavage of tetraalkylhydrazines using either the oxidative or reduction cleavage methods mentioned above.

To test the first strategy, we prepared the dienes **2a** and **16**[22] (Figure 5.3) and tested their ability to undergo the aza-Diels-Alder reaction involving dienophile **3**. Despite significant efforts, no desired cycloaddition adduct was obtained probably due to the lower reactivity of these dienes, which are less electron rich.

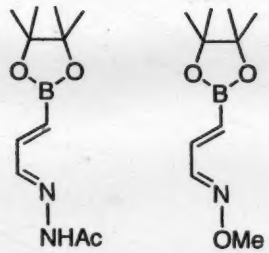


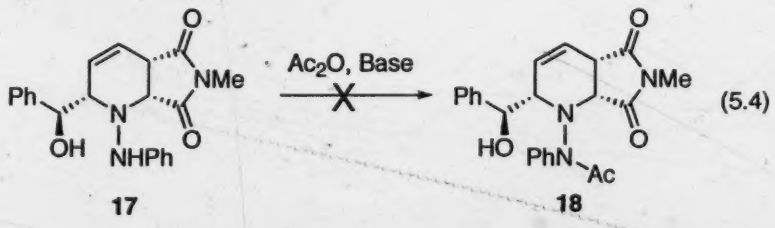
Figure 5.3. Use of activated dienes towards hydrazine cleavage.

We next examined the activation of the hydrazine moiety following the MCR/retro-ene sequence. To this end, two main strategies were envisioned:

a). A direct activation of trisubstituted hydrazines

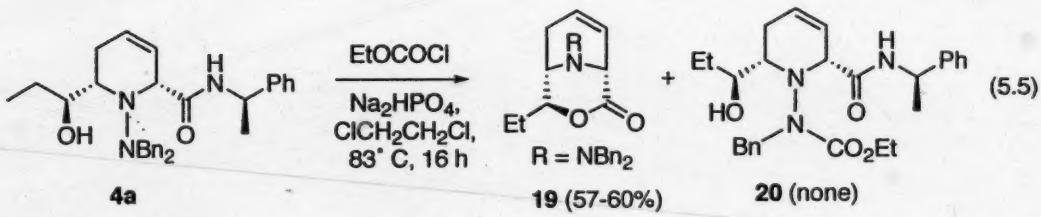
b). An indirect route taking advantage of the well established *N*-debenzylation of tertiary amines using chloroformates. It should be noted that this strategy had never been applied to hydrazines before.[23,24,25]

To test the former strategy, compound **17** was chosen as model substrate. However, all attempts to acylate **17** employing a variety of bases (*n*-BuLi, NaH) only met with failure (Equation 5.4). In general, the substrate was either unreactive or was prone to decomposition under the reaction conditions.



We next synthesized the 1-dibenzylamino piperidine **4a** (see Chapter 4 for the synthesis of this class of compounds). It was hoped that, in a manner similar to that of tertiary benzyl amines, this compound would undergo a debenzylation/carbamoylation

reaction sequence upon treatment with the appropriate chloroformate reagents. However, when the latter was treated with ethylchloroformate[23,24] or α-chloro ethylchloroformate[25] under known reaction conditions, none of the expected debenzylated product **20** was obtained (Equation 5.5). Instead, an intramolecular lactonization product **19**, resulting from the internal displacement of the activated secondary amide, was observed.

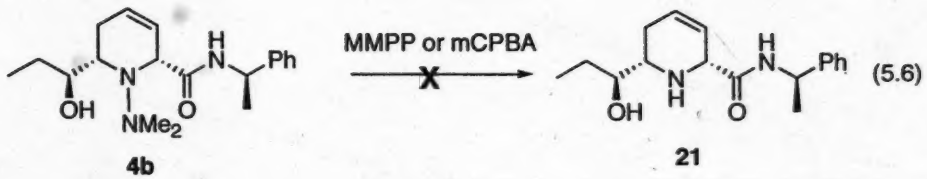


4a **19** (57-60%) **20** (none) (5.5)

These failures prompted us to explore the use of more direct strategies and these efforts are summarized next.

5.2.1.2 Direct oxidative N-N fragmentation strategy

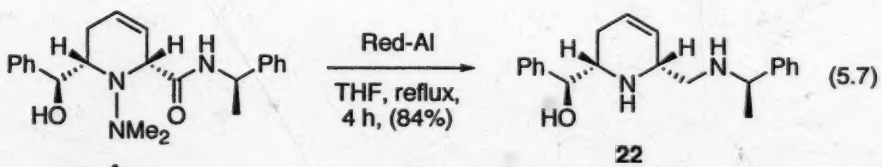
Our first attempt relied on the oxidative cleavage methodology described above.[19,20] Based on the proposed mechanism for this reaction, we reasoned that the oxidant would preferentially react with the least hindered exocyclic nitrogen, hence leading to a selective N-N fragmentation. In this approach, the high reactivity of the nitrogen towards electrophilic peroxide reagents should also preclude any competitive epoxidation of the C3-C4 olefin. However, when we put this hypothesis to the test with substrate **4b** under various reaction conditions (e.g. MMPP, mCPBA), only decomposition products were observed (Equation 5.6).



4b 21

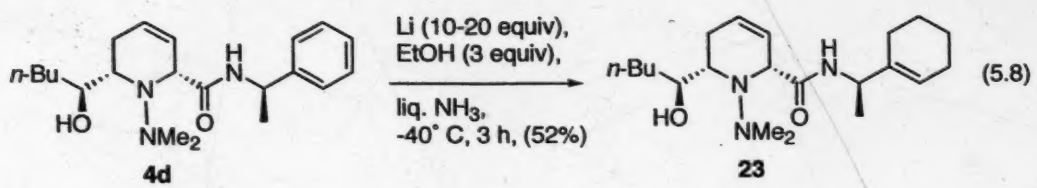
5.2.1.3 Direct reductive N-N fragmentation strategy

As in the case of the oxidative fragmentation, treatment of **4b** with zinc, a reductive N-N cleavage method,[26] did not yield any of the desired N-N cleaved product. On the other hand, powerful reducing agents like Red-Al did yield the desired N-N cleavage product **22.** Unfortunately, the carbonyl functionality could not be preserved during this operation, thereby rendering the one carbon homologation difficult (Equation 5.7).



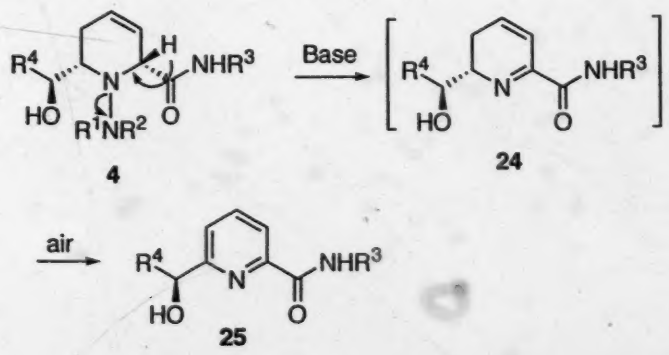
4c 22

Finally, attempts to achieve the one-pot amide debenzylation/N-N cleavage of **4d** under Bouveault-Blanc-type conditions, and variants thereof,[27] only resulted in the reduction of the aromatic moiety to afford **23**. The latter result further emphasizes the difficult challenge that represents the cleavage of tetraalkylhydrazines (Equation 5.8).



5.2.2 Design of a non-reductive hydrazine cleavage strategy.

As stated previously, the failures of traditional N-N cleavage methods with tetraalkylhydrazines such as **4d** exposed an important methodological gap in organic synthesis. A potential solution to this problem arose from understanding the reactivity of compounds of type **4**. For instance, we had realized that these compounds are unstable to bases. Indeed, treatment of **4** with bases such as Et_3N or DBU results in the effective cleavage of the N-N bond to give **25**, presumably via deprotonation of the acidic C2 proton, followed by atmospheric oxidation (Scheme 5.3).



Scheme 5.3. Base-induced aromatization of compounds of type **4**.

Along this line, we anticipated that compounds **26** could be obtained if a suitable anion precursor could be introduced next the to the exocylic nitrogen. After careful consideration, we chose to attach a Me_3SiCH_2- substituent to the exocyclic nitrogen and

test the feasibility of a fragmentation process reminiscent of the removal of a [2-(trimethylsilyl)ethoxy]methyl (SEM) protective group,[28,29] (Figure 5.4). Unfortunately, this type of silylated hydrazine was not known in the literature. The discovery of a convenient synthetic route to this class of reagent became the next focus of our efforts.

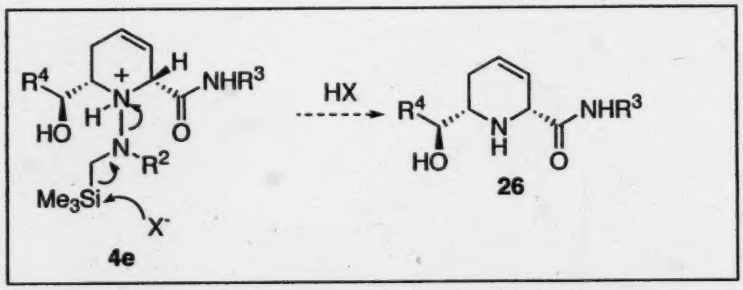
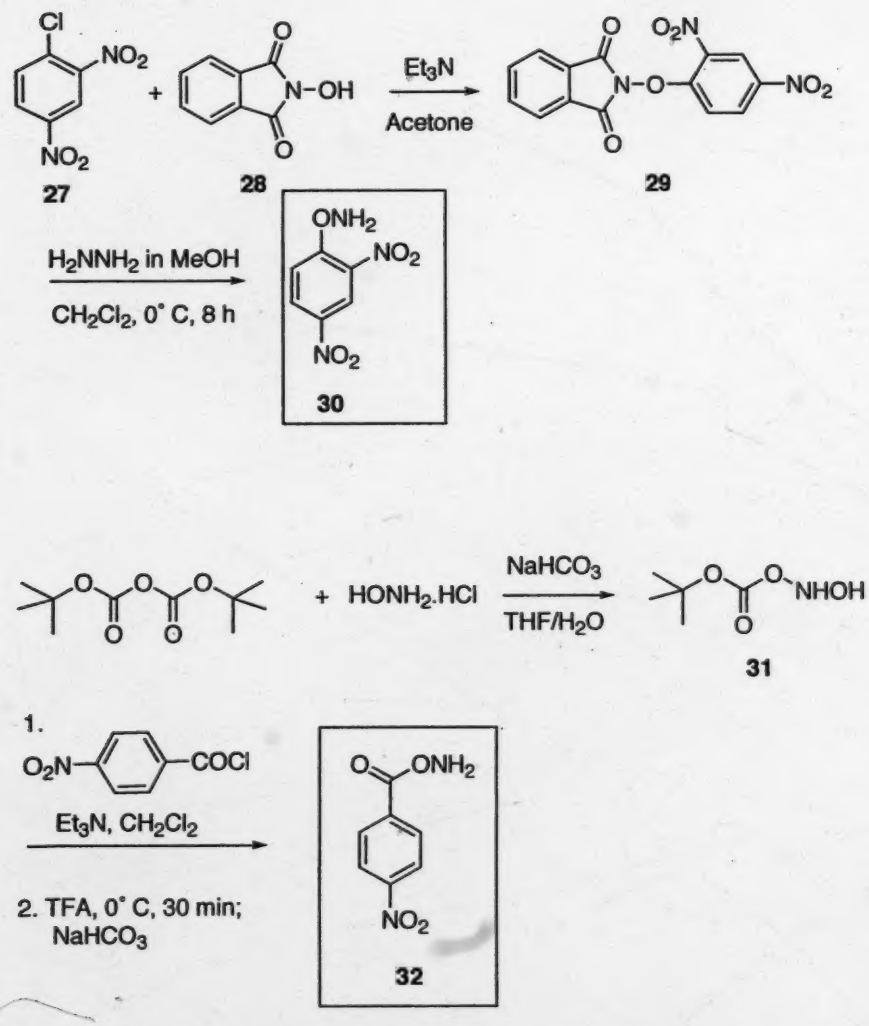


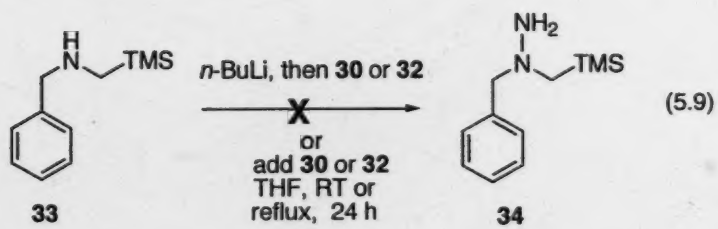
Figure 5.4. Proposed hydrazine fragmentation strategy

5.2.3 Development of a synthetic route to hydrazine 34.

At first, we thought that compounds of type **34** (Equation 5.9) could be synthesized via a direct *N*-amination strategy. Our interest in developing such a methodology was piqued by the lack of literature precedent. For the purpose, known amination reagents **30**[30] and **32**[31] were synthesized (Scheme 5.4) and reacted with lithium (trimethylsilyl)methyl benzylamide generated *in situ*. However, none of the desired *N*-amination product **34** was observed (Equation 5.9).

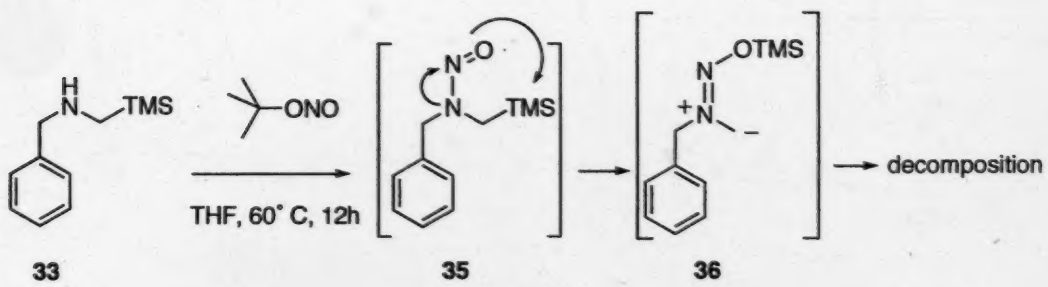


Scheme 5.4. Synthesis of aminating reagents **30** and **32**.



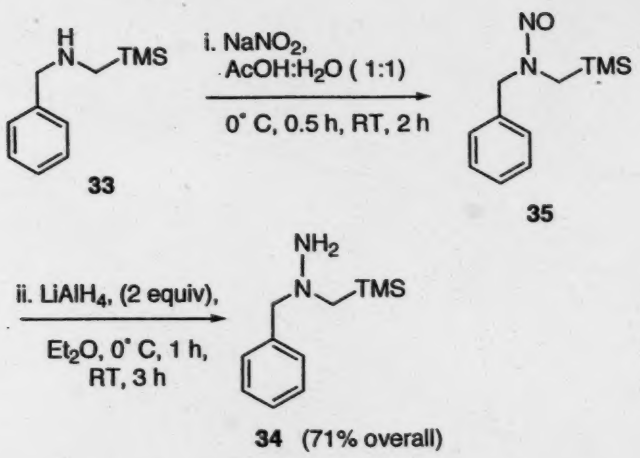
(5.9)

We then turned our attention to a two step synthetic strategy which first involved submitting the amine to *N*-nitrosation reaction conditions followed by reduction of the nitroso group. Accordingly, the commercially available (trimethylsilyl)methyl benzylamine **33** was treated with *t*-butyl nitrite (Scheme 5.5). This reaction did not yield any of the desired product. Compounds of type **35** are indeed prone to ylid formation, which can be trapped with alkenes to afford [3+2] cycloaddition adducts under thermal conditions.[32]



Scheme 5.5. Attempted synthesis of nitroso compound **35**.

Finally, we explored a standard amine nitrosation method consisting of treating the amine with sodium nitrite in an aqueous solution of acetic acid (Scheme 5.6). The unstable nitroso intermediate **35** undergoes slow decomposition at room temperature, which can be accelerated by heating. Consequently, it was rapidly reduced to the desired hydrazine **34** at a low temperature. The latter was obtained in sufficiently high purity that it could be carried through the next step without the need for any purification. Alternatively, the hydrazine could also be purified by simple acid-base extraction or bulb-to-bulb distillation.



33 **35**

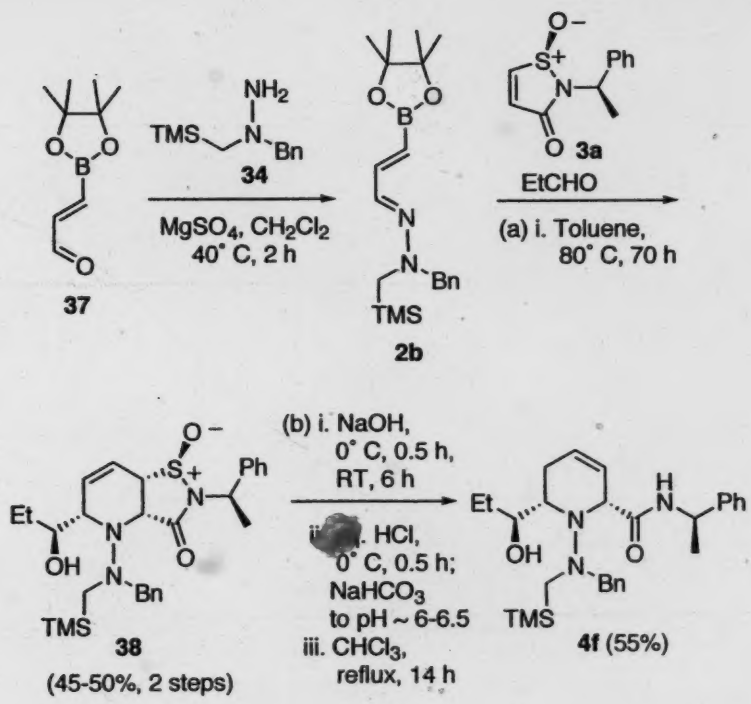
34 (71% overall)

Scheme 5.6. Synthesis of 1-(trimethylsilylmethyl)-1-benzylhydrazine.

5.2.4 Synthesis of (-)-methyl palustramate (1).

5.2.4.1 Construction of the [4+2]/allylboration/retrosulfinyl-ene adduct 4f.

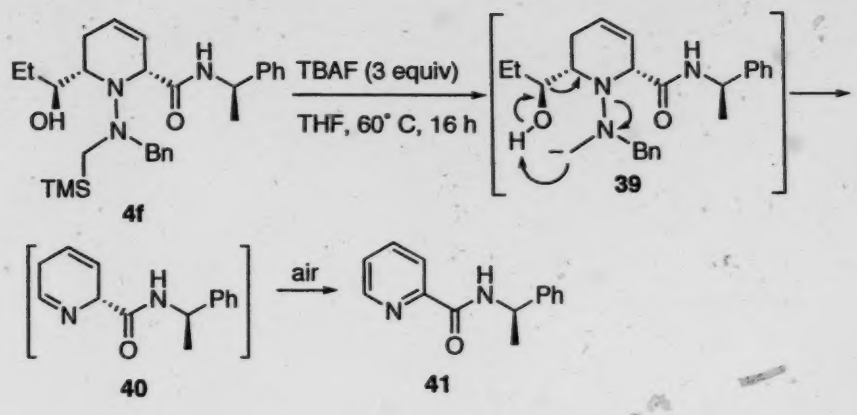
Hydrazine **34** was first condensed with 3-boronoacrolein **37** in refluxing dichloromethane under dehydrating reaction conditions to afford the diene **2b** as a mixture of different geometrical isomers. The latter was carried through the three-component [4+2]/allylboration reaction involving dienophile **3a** and freshly distilled propionaldehyde (Scheme 5.7). The MCR-adduct **38** was obtained as a single stereoisomer albeit in moderate yield due to partial decomposition of the product under the conditions involving long reaction times. Compound **38** was then submitted to our optimal conditions for the retro-sulfinyl-ene reaction to afford key intermediate **4f**. This compound was found to be slightly unstable on silica gel, and as such it was best carried through the next step without any purification from **38**. The stage was now set for testing the crucial hydrazine cleavage strategy.



Scheme 5.7. Sequential aza[4+2]/allylboration route to the key hydrazine cleavage precursor **4f**.

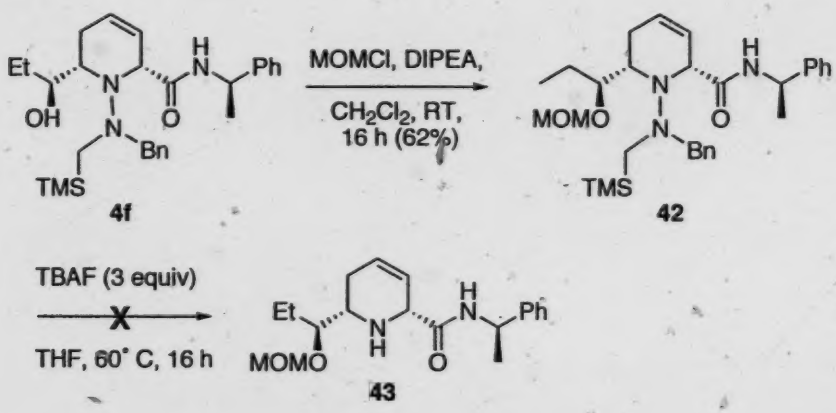
5.2.4.2 Chemoselective N-N fragmentation studies of the key hydrazine cleavage precursor 4f.

We first explored the tetrabutylammonium fluoride (TBAF) mediated desilylation reaction conditions.[28,29] Compound **4f** was heated overnight in THF in the presence of three equivalents of TBAF. To our dismay, after work-up, the ^{1}H NMR spectrum of the crude product revealed a clean conversion of the starting material to pyridine **41**, which is consistent with a C-C fragmentation reaction via the proposed mechanism depicted in Scheme 5.8.



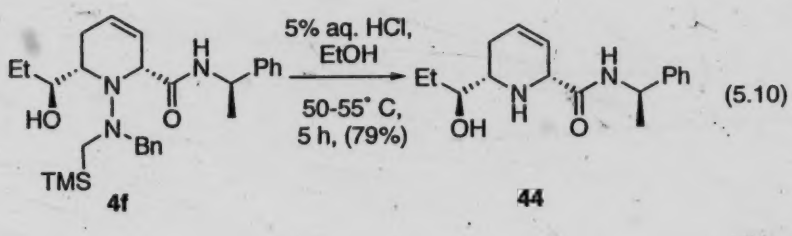
Scheme 5.8. Undesired TBAF promoted C-C cleavage.

In order to prevent the reaction from proceeding via this undesired pathway, the alcohol was protected as its methoxymethyl (MOM) ether **42**. However, when **42** was submitted to the above reaction conditions, none of the desired product **43** was obtained (Scheme 5.9).



Scheme 5.9. Attempted TBAF promoted N-N cleavage using MOM-protected substrate **42**.

We then turned our attention to using acid promoted desilylation conditions.[29] Gratifyingly, when key intermediate **4f** was stirred in ethanolic aqueous HCl solution, a very clean conversion of the starting hydrazine to the desired product **44** along with benzylamine side product were observed in the NMR of the crude reaction mixture (Equation 5.10).



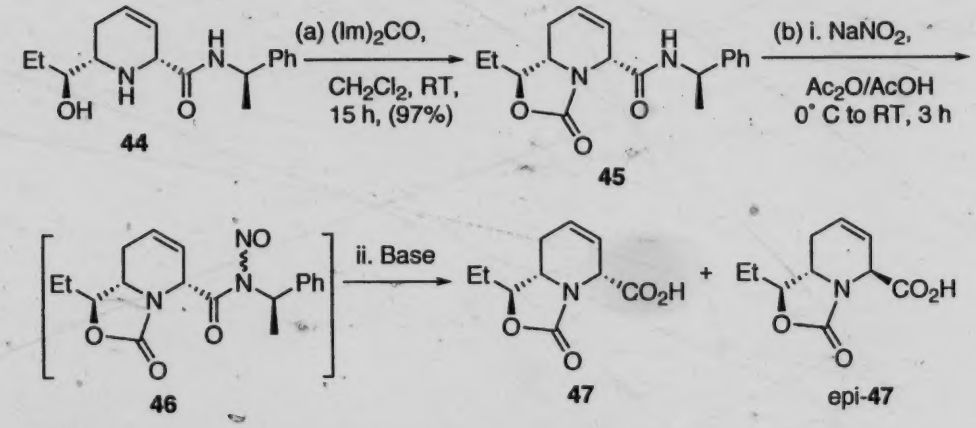
(5.10)

5.2.5 Completion of the synthesis of methyl palustramate (1).

With this key N-N cleaved product **44** in hand, we next addressed the one carbon homologation issue that we hoped to accomplish via the previously described Arndt-Eistert reaction sequence (Chapter 4). For this purpose, the amino alcohol **44** was first converted in excellent yield to its carbamate derivative **45** using carbonyl diimidazole (Table 5.1). Selective hydrolysis of the amide group could only be performed through formation of the *N*-nitroso derivative **46**.[33,34] Unfortunately, epimerization occurred at C2 in this operation, and the desired 2,6-*cis*-configured acid product **47** was only obtained as the minor isomer in a 1:2 ratio. This result contrasted with our earlier observations with the saturated analogue, whereby the 2,6-*cis*-piperidine was always observed as the major product for a nitrosation time of three hours or less (Chapter 4). It is interesting to note that the nitroso compound **46** is prone to epimerization even in the absence of any external base. Indeed, complete inversion of the C2 stereochemistry could be observed by

simply maintaining a chloroform solution of **46** at room temperature overnight. Moreover, when *N*-nitrosation was allowed to proceed at room temperature for longer reaction times, the undesired 2,6-*trans*-isomer epi-**47** was obtained almost exclusively. In order to reverse this trend, we thus set out to investigate the effect of base and temperature on the stereochemical outcome of this hydrolysis reaction. The results are summarized in Table 5.1.

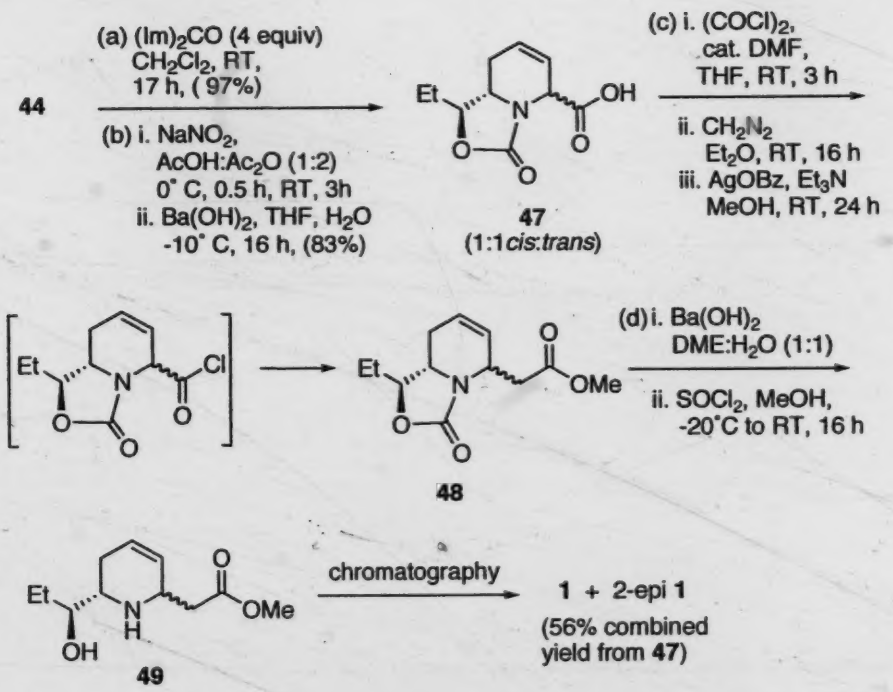
Table 5.1. Optimization of the hydrolysis of amide **45**.



Entry	Base	Temperature (°C)	Time (h)	Ratio[a] 47:epi-47
1	NaOH	23	16	1:7
2	KOH	23	16	1:4
3	LiOH	23	16	1:5
4	$Ba(OH)_2$	23	16	1:2.3
5	$Ba(OH)_2$	0	8	1:1.6
6	$Ba(OH)_2$	-10	16	1:1
7	LiOOH	0	8	1:1
8	LiOOH	-10	15	3.3:1

The reaction was performed on a 10-15 mg of **46**. [(a)]The ratio of **47**:epi-**47** was determined by proton NMR of the crude reaction mixture after work-up.

The best result was obtained at low temperature using the highly nucleophilic lithium hydrogen peroxide previously reported by Evans and coworkers (Entry 8, Table 5.1).[34] However, in this case, the product was always contaminated by an inseparable pyridine by-product. Thus, for the completion of the synthesis, we opted to use the barium hydroxide conditions, which provided a clean reaction with a 1:1 ratio of C2 epimers (Entry 6, Table 5.1). The required homologation step was then performed on this 1:1 epimeric mixture of carboxylic acids **47** under Arndt-Eistert reaction conditions (Scheme 5.10). The two epimers **48** were directly subjected to the final step of aminoalcohol deprotection with the method of Weinreb and co-workers using barium hydroxide.[35] Re-esterification of the resulting amino acid and effective chromatographic separation afforded (-)-methyl palustramate (**1**), which possessed spectral characteristics and an optical rotation value in agreement with reported literature data.[36]

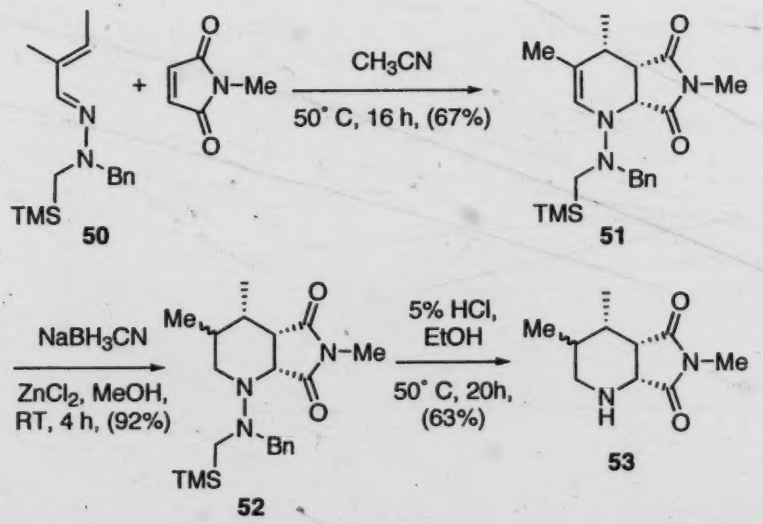


Scheme 5.10. Synthesis of (-)-methyl palustramate (**1**).

5.2.6 Preliminary study of the scope and mechanism of the hydrazine cleavage method.

The C-C fragmentation during the TBAF promoted N-N cleavage (i.e. **4f** to **41**) prompted us to investigate any possible role for the proximal side chain alcohol under the hydrazinolysis conditions. Towards this goal, bicyclic compound **51** was prepared via an aza-Diels-Alder reaction between diene **50** and *N*-methyl maleimide (Scheme 5.11). The sodium cyanoborohydride reduction of the enamine **51** resulted in a 2:1 diastereomeric mixture at the methyl stereocenter, which was inconsequent for our study. When compound **52** was subjected to our N-N cleavage conditions the desired reaction product **53** was obtained in a non-optimized yield of 63%. The reaction time, however, was significantly longer compared to the cleavage of **4f**. In light of this result, it seems

plausible that the alcohol functionality in the α-hydroxyalkyl derivative **4f** participates and accelerates the N-N cleavage via nucleophilic attack of the silicon atom in an intramolecular fashion. In the case of substrate **52**, the N-N fragmentation must proceed via an intermolecular nucleophilic attack. In this scenario, ethanol or the chloride anion could serve as nucleophiles. This intramolecular reaction will be expected to proceed at a much lower rate than the intermolecular counterpart. The use of aprotic solvent or a bulky acid should shed more light on this mechanistic proposal. Considering the failure of the TBAF-promoted method, protonation of the endocyclic nitrogen seems essential for a successful N-N cleavage in this context. These results suggest a wide scope of application for this novel and acid-cleavable hydrazine.



Scheme 5.11. Construction of model compound **52** for investigation of the scope and mechanism of the hydrazine cleavage methodology.

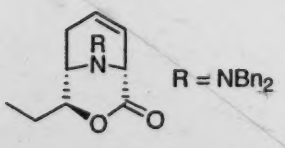
5.3 Conclusion

In summary, we have applied our aza[4+2]cycloaddition/allylboration/retro-sulfinyl-ene sequential reaction to the enantioselective synthesis of the palustrine relative (-)-methyl palustramate (**1**). The entire sequence to reach target **1** was accomplished with only two purification steps, and in only ten linear synthetic operations from commercial 3,3'-diethoxypropyne.[37] Along the way, we have developed the first class of hydrazines that can be cleaved non-reductively under mild acidic conditions in the presence of unsaturations. This new methylsilylated-hydrazine played a pivotal role in the completion of the synthesis of **1**. Further applications of this class of hydrazines including the development of a chiral variant are currently under investigation in the Hall laboratory.

5.4 Experimental

The methods described in Section 2.4 (Chapter 2) also apply here with the following additions. The synthesis and characterization data for compound **17** was previously reported by Jyoti Tailor.[38] Compound **18** was prepared by Agnieszka Ulazyck-Lesanko.[39] The synthesis of dienophile **3a** was described in Chapter 3. The syntheses of compounds **4a-c** were reported in Chapter 4 of this thesis.

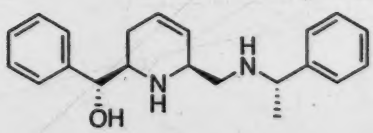
5.4.1 Rac-(*1S,4R,5S*)-9-Dibenzylamino-4-ethyl-3-oxa-9-aza-bicyclo[3.3.1]non-7-en-2-one (19)



Amide **4a** (68.0 mg, 0.14 mmol) was dissolved in 4 mL of 1,2-dichloroethane, ethyl chloroformate (0.046 ml, 0.420 mmol) and Na_2HPO_4 (3 equiv) were added and the resulting suspension was refluxed for 24 h, then cooled to RT. The mixture was diluted with more solvent and washed with water, then brine. The solution was dried over magnesium sulfate. The solvent was removed, followed by silica gel chromatography to afford product **19** as a colorless oil (30 mg, 58%).

TLC (25%, EtOAc/hexane, $KMnO_4$, PMA): 0.48; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33-7.18 (m, 10H); 6.05-5.97 (m, 2H), 4.17 (d, *J* = 4.7 Hz, 1H), 3.90 (d, *J* = 12.9 Hz, 2H), 3.79 (dt, *J* = 2.0, 6.9 Hz, 1H), 3.60 (d, *J* = 12.9 Hz, 2H), 3.21 (d, *J* = 4.9 Hz, 1H), 2.52 (dm, *J* = 18.3 Hz, 1H), 1.80 (dd, *J* = 4.6 Hz, 18.2, 1H), 1.35 (app sept, *J* = 7.5 Hz, 1H), 1.18 (app sept, *J* = 7.2 Hz, 1H), 0.85 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.0, 139.0, 130.2, 128.9, 128.2, 127.0, 126.0, 124.9, 86.5, 57.9, 55.5, 53.9, 29.4, 28.3, 9.7; IR (CH_2Cl_2 cast) ν_{max} = 3085, 3061, 3029, 2966, 2934, 2877, 2835, 1739, 1673, 1601, 1494, 1453, 1430, 1368 cm^{-1}; HRMS (ES): *m/z*: calcd for $C_{23}H_{26}N_2O_2Na$: 385.1892; found: 385.1889 $[M+Na]^+$.

5.4.2 Rac-(*2R,6R*)-6-[(*S*)-Hydroxybenzyl]-2-[*(R)*-methylbenzylamino]methyl-1,2,5,6-tetrahydropyridine (22)

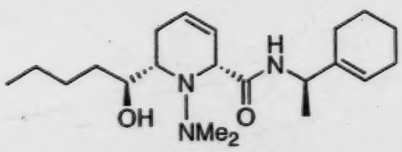


Amide **4d** (50 mg, 0.13 mmol) was dissolved in 5 mL of THF and Red-Al (0.13 mL, 65% wt/v in toluene) was added and the resulting yellowish solution was refluxed for 12 h. The reaction was cooled to room temperature, water was slowly added and the resulting

suspension was filtered. The solvent was evaporated to dryness under reduced pressure and the product was purified by acid-base extraction to give **22** as a colorless oil (41 mg, 84%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39-7.19 (m, 10H), 5.74-5.66 (m, 1H), 5.53 (dm, *J* = 10.3 Hz, 1H), 4.37 (d, *J* = 8.1 Hz, 1H), 3.77 (q, *J* = 7.2 Hz, 1H), 3.42-3.37 (m, 1H), 2.86 (ddd, *J* = 4.1, 7.9, 12.1 Hz, 1H), 2.58-2.52 (m, 2H), 2.51-2.38 (bs, 2H), 1.91-1.78 (m, 1H), 1.64-1.52 (m, 1H), 1.36 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.9, 141.3, 128.5, 128.3, 128.2, 127.9, 127.1, 126.9, 126.6, 126.2, 77.3, 58.7, 58.6, 54.5, 52.3, 28.1, 23.8; MS (ES): *m/z*: calcd for $C_{21}H_{26}N_2O$; 322.20 found: 323.21 $[M+H]^+$.

5.4.3 Rac-(*2R,6S*)-1-Dimethylamino-6-[(*S*)-hydroxypentyl]-1,2,5,6-tetrahydropyridine-2-carboxylic acid-[(*R*)-cyclohex-1-enyl-ethyl)-carboxamide (23)

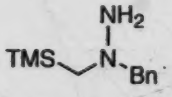


Lithium (6 mg, 0.83 mmol) was dissolved in liquid ammonia at –78° C. Anhydrous ethanol (0.02 mL) was added, followed by a solution of substrate **4c** (39 mg, 0.11 mmol) in 0.5 mL of THF after 10 min. At the end of the addition, the solution turned colourless, another 6 mg of lithium was added to reinstate the initial deep blue coulour. The reaction mixture was stirred in refluxing ammonia for 4 h, then brought to RT and saturated ammonium chloride was added slowly. The aqueous solution was extracted twice with ethyl acetate. The combined organic layers was washed with water, brine, then dried over

magnesium sulfate and concentrated on the rotary evaporator. The residue was purified on silica gel to afford the product **23** as a film (20 mg, 52%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35 (d, *J* = 8.1 Hz, 1H), 7.02 (bs, 1H), 5.72-5.58 (m, 3H), 4.40 (app p, *J* = 7.3 Hz, 1H), 3.54 (dt, *J* = 2.1, 7.9 Hz, 1H), 3.45 (app t, *J* = 5.1 Hz, 1H), 2.72-2.56 (m, 5H), 2.40 (s, 6H), 2.24-2.16 (m, 1H), 1.76-1.64 (m, 3H), 1.60-1.26 (m, 6H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.11-1.01 (m, 1H), 0.90 (t, *J* = 7.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.2, 135.8, 124.2, 123.8, 119.3, 78.1, 58.2, 55.4, 49.2, 33.8, 27.2, 26.59, 26.55, 23.9, 22.97, 22.94, 19.2, 17.1, 14.1; HRMS (ES): *m/z*: calcd for $C_{21}H_{37}N_3O_2Na$: 386.2783; found: 386.2780 $[M+Na]^+$.

5.4.4 *N*-Benzyl-*N*-(trimethylsilylmethyl)-hydrazine (34)

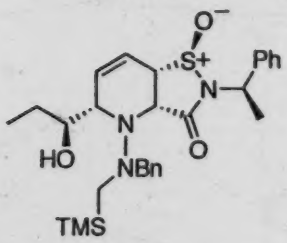


1-(trimethylsilylmethyl)benzylamine **33** (5.0 g, 2.6 mmol) was added to an ice cold acetic acid:acetic anhydride (1:1, 100 mL) solution. Sodium nitrite (5.4 g, 7.8 mmol) was added over 10 min and the solution was stirred for 1 h then brought to RT and stirred for an additional 2 hours. Ethyl ether (100 mL) was added and the solution was transferred to a separatory funnel. The two layers were separated and the aqueous layer was further extracted twice with ether (100 mL, twice). The combined organic layers were washed successively with water, sodium bicarbonate and brine. The solution was dried over magnesium sulfate, filtered and the solvent was evaporated under reduced pressure at room temperature to afford the nitroso intermediate **35** as a yellowish oil, which was kept under high vacuum for few hours in order to remove any acetic acid/anhydride impurity.

A suspension of $LiAlH_4$ (1.7 g, 44 mmol) in 50 mL of ether was refluxed for an hour then cooled on ice and a solution of the nitroso intermediate **35** in ether (60 mL) was added slowly over an hour. The resulting suspension was stirred on ice for 1 h, then brought to RT and stirred for an additional 2 h. The excess LAH was quenched by slow addition of water until the precipitates became completely white. The solid was removed by filtration and washed several times with ether. The filtrate was washed with water then brine and dried over magnesium sulfate. The solvent was evaporated to afford hydrazine **34** as a colorless oil. The hydrazine was of sufficient purity to be carried through to the next step without any purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42-7.27 (m, 5H), 3.61 (s, 2H), 2.84-2.56 (bs, 2H), 2.22 (s, 2H), 0.12 (s, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.3, 129.2, 128.5, 127.3, 126.9, 70.4, 53.0, -1.2; IR (CH_2Cl_2 film) ν_{max} = 3293, 3085, 3062, 3028, 2951, 2840, 2787, 1948, 1809, 1677, 1604, 1494, 1358, 1246, 1199 cm^{-1}; MS (ES): *m/z*: calcd for $C_{11}H_{20}N_2Si$: 208.14 found: 209.14 $[M+H]^+$.

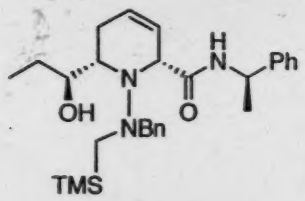
5.4.5 (*1R,3aR,5R,7aR*)-1-[(Trimethylsilyl)methylbenzylamino]-5-[(*S*)-hydroxypropyl]-6-(*R*-methylbenzyl)-3a,4,5,7a-tetrahydro-isothiazolo[3,4-b]pyridin-3-(2H)-one-1-oxide (38)



3-boronoacrolein (1.14 g, 6.3 mmol) was dissolved in 30 mL of dichloromethane and hydrazine **34** (1.3 g, 6.3 mmol) was added slowly at RT. Magnesium sulfate (1.3 equiv) was added to the reaction mixture and the resulting suspension was refluxed for 2 h, cooled to RT and filtered using a pre-dried fritted funnel. The solvent was removed under reduced pressure to afford a brown oil which was then dissolved in toluene (30 ml) in a high pressure reaction vessel. Homochiral dienophile **3a** (1.39 g, 6.3 mmol) was added, followed by freshly distilled propionaldehyde (2.5 mL, 31.0 mmol). The tube was capped and heated to 85° C for 70 h under vigorous stirring. The reaction mixture was allowed to cool to room temperature and saturated aqueous $NaHCO_3$ was added. The mixture was stirred for 30 min, then the two layers were separated. The aqueous phase was extracted with ethyl acetate (2 × 50 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by flash chromatography to afford **38** as a thick brown oil (1.6 g, 47% yield).

TLC (25%, EtOAc/hexane, $KMnO_4$, PMA):0.34; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41-7.09 (m, 10H), 6.08 (ddd, *J* = 2.2, 4.0, 10.7 Hz, 1H), 5.81 (d, *J* = 10.7 Hz, 1H), 5.39 (q, *J* = 7.3 Hz, 1H), 4.89 (d, *J* = 7.0 Hz, 1H), 3.73-3.78 (bs, 1H), 3.70 (d, *J* = 14.0 Hz, 1H), 3.64 (d, *J* = 14.1 Hz, 1H), 3.22-3.16 (m, 1H), 3.18-3.08 (bs, 1H), 2.36 (d, *J* = 13.9 Hz, 1H), 2.34-2.30 (m, 1H), 2.16 (d, *J* = 13.8 Hz, 1H), 1.80 (d, *J* = 7.3 Hz, 3H), 1.39-1.29 (m, 1H), 1.26-1.16 (m, 1H), 0.82 (t, *J* = 7.3 Hz, 3H), 0.13 (s, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.9, 140.0, 138.6, 135.4, 128.9, 128.5, 128.3, 128.0, 127.2, 126.9, 117.0, 73.1, 60.5, 58.9, 58.4, 53.6, 45.9, 25.9, 19.9, 10.0, -1.5; ; IR (CH_2Cl_2 cast) ν_{max} = 3500, 3062, 3031, 2959, 1712, 1603, 1495, 1454, 1379, 1027 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{28}H_{39}N_3O_3SSi$: 525.25; found: 548.2372 $[M+Na]^+$

5.4.6 (*2R,6S*)-1-[(Trimethylsilyl)methylbenzyl]amino]-6-[(*S*)-hydroxypropyl]-1,2,5,6-tetrahydropyridine-2-carboxylic acid-[(*R*)-methylbenzyl]amide (4f)

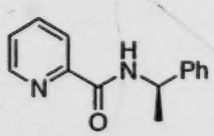


Compound **38** (0.61 g, 1.20 mmol) was dissolved in 6 mL of acetone at 0° C. Cold 5% aqueous NaOH solution (10 mL) was added and the reaction mixture was stirred for 30 min, then brought to room temperature and stirred for 6 h. The solution was cooled again on ice and 10% aqueous HCl solution was added over 20 min (final pH ~ 1). Stirring was continued for an additional 30 min, then 5% aqueous $NaHCO_3$ was added slowly until pH 6.0-6.5. The solvent was evaporated to dryness and $CHCl_3$ (60 mL) was added to the resulting solid. The suspension was stirred for 5 min prior to the addition of $MgSO_4$. All solid particles were removed by filtration and the filtrate was refluxed for 16 h. The reaction mixture was then cooled to room temperature and the solvent was removed under reduced pressure. The resulting colorless oil was purified by flash chromatography to afford **4f** as a yellowish oil (0.29 g, 53%).

TLC (25%, EtOAc/hexane, $KMnO_4$, PMA):0.26; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.48-7.43 (m, 1H), 7.38-7.34 (m, 2H), 7.33-7.27 (m, 3H), 7.20-7.05 (m, 5H), 6.30-6.24 (m, 1H), 5.88-5.84 (m, 1H), 5.05 (app p, *J* = 7.1 Hz, 1H), 4.70 (d, *J* = 5.7 Hz, 1H), 4.20 (bs, 1H), 3.57 (d, *J* = 14.5 Hz, 1H), 3.44 (d, *J* = 14.5 Hz, 1H), 3.21-3.13 (m, 1H), 3.02-2.96 (m, 1H), 2.30 (d, *J* = 14.1 Hz, 1H), 2.28-2.22 (m, 1H), 2.19 (d, *J* = 14.1 Hz, 1H), 1.90

(dm, J = 17.5 Hz, 1H), 1.48-1.38 (m, 1H), 1.24 (t, J = 7.0 Hz, 3H), 1.22-1.16 (m, 1H), 0.82 (t, J = 7.3 Hz, 3H), 0.09 (s, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3, 143.5, 139.5, 128.8, 128.7, 127.6, 127.4, 127.2, 127.1, 126.4, 126.2, 124.8, 72.1, 68.2, 63.2, 61.3, 55.4, 48.6, 26.6, 22.6, 20.4, 8.8, -1.2; IR ($CHCl_3$ cast) ν_{max} = 3275, 3062, 3030, 2955, 2875, 1651, 1643, 1604, 1585, 1574, 1520, 1504, 1495, 1452, 1419, 1366, 1322, 1248 cm^{-1}; HRMS (EI): m/z: calcd for $C_{28}H_{42}N_3O_2Si$: 480.3041 found: 480.3041 $[M]^+$; $[\alpha]_D^{23}$ = +70.3 (c = 0.97 in $CHCl_3$)

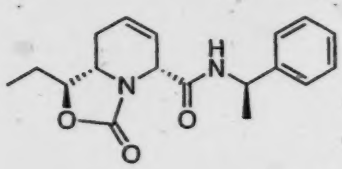
5.4.7 Rac-Pyridine-2-[(*R*)-methylbenzyl]-carboxamide (41)



Compound **4f** (18 mg, 0.04 mmol) was dissolved in 3 mL of THF, and a 1M solution of TBAF in THF (0.19 mL, 0.19 mmol) was added. The solution was heated for 15 h at 60° C then cooled to RT and the solvent was evaporated. The residue was purified by silica gel chromatography to afford **41** as a colourless film (7 mg, 81%).

TLC (20%, EtOAc/hexane, UV): 0.13; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.54 (ddd, J = 0.9, 1.7, 4.9 Hz, 1H), 8.33 (bs, 1H), 8.21 (dm, J = 7.8 Hz, 1H), 7.84 (app dt, J = 1.7, 7.7 Hz, 1H), 7.44-7.24 (m, 6H), 5.33 (app p, J = 6.7 Hz, 1H), 1.63 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.5, 150.0, 148.1, 143.4, 137.4, 128.7, 127.4, 126.3, 126.2, 122.4, 48.9, 22.1; IR (CH_2Cl_2 film) ν_{max} = 3381, 3059, 3028, 2972, 2929, 1674, 1590, 1513, 1464, 1433 cm^{-1}; HRMS (ES): m/z: calcd for $C_{14}H_{15}N_2O$: 227.1179 found: 227.1178 $[M+H]^+$.

5.4.8 9-(*1S,4aS,8aS*)-1-Ethyl-(4a,4,8,8a)-tetrahydro-3-oxo-4H-oxazolo[3,4-a]-5-carboxylic-(*R*-methylbenzyl)carboxamide (45)

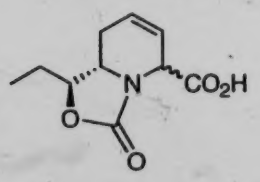


Compound **44** (1.0 g, 2.1 mmol) was dissolved in 95% ethanol (60 mL) and 10% aqueous HCl (7.2 mL) was added at room temperature. The resulting solution was heated to 50° C for 5 h, then cooled to room temperature. The solvent was evaporated under reduced pressure and the residue was cooled on ice and treated with 5% aqueous NaOH solution until the solution was basic. Ethyl acetate was added and the biphasic mixture was transferred to a separatory funnel. The two layers were separated and the aqueous layer was further extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under vacuum. The resulting brown residue was left on the high-pressure vacuum pump for 2 h, and then dissolved in CH_2Cl_2 (25 mL). Carbonyl diimidazole (4 equiv) was added and the mixture was stirred at room temperature overnight. The solution was diluted with 40 ml of CH_2Cl_2, then washed with 10% aqueous HCl, and brine. The organic layer was dried over magnesium sulfate, filtered and the solvent removed to afford a white solid. Recrystallization from ethyl acetate/hexane afforded the pure product as a colorless oil (0.64 g, 97%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41-7.19 (m, 5H), 6.38 (d, *J* = 7.5 Hz, 1H), 5.99-5.95 (m, 1H), 5.79 (dm, *J* = 10.7 Hz, 1H), 5.11 (app p, *J* = 7.4 Hz, 1H), 4.46-4.42 (m, 1H), 4.22-4.10 (m, 1H), 3.41 (dt, *J* = 4.3, 8.2 Hz, 1H), 2.39-2.25 (m, 2H), 1.82-1.72 (m, 2H),

1.48 (d, J = 7.3 Hz, 3H), 1.04 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.7, 157.6, 142.8, 128.6, 127.3, 126.3, 125.0, 124.5, 83.5, 57.9, 57.6, 49.0, 28.5, 25.9, 21.4, 9.4; IR (CH_2Cl_2 cast) ν_{max} = 3291, 3061, 2971, 2934, 1757, 1544, 1494, 1450, 1415, 1375, 1307, 1266, 1223 cm^{-1}; HRMS (ES): *m/z*: calcd for $C_{18}H_{22}N_2O_3$: 314.1787; found: 337.15282 $[M+Na]^+$; elemental analysis calcd (%) for $C_{18}H_{22}N_2O_3$ (314): C 68.77, H 7.05, N 8.91; found: C 68.57, H 7.33, N 8.81; $[\alpha]_D^{23}$ = +165.8 (c = 0.23 in $CHCl_3$

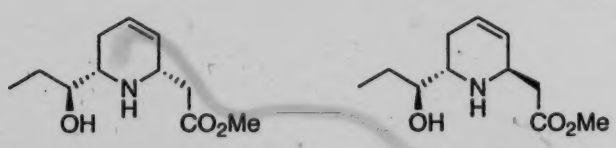
5.4.9 -(*1S,4aS,8aS*)-1-Ethyl-(4a,4,8,8a)-tetrahydro-3-oxo-4H-oxazolo[3,4a]-5-carboxylic (47)



Carbamate **45** (0.23 g, 0.73 mmol) was dissolved in 9 mL of AcOH/Ac_2O (1:2) and cooled to 0° C. Sodium nitrite (0.5 g, 7.2 mmol) was added in one portion. The initially colourless solution turned green after a few minutes. The reaction mixture was stirred on ice for 30 min, then brought to room temperature and stirred for an additional 3 h. The reaction mixture was diluted with water and ethyl acetate, transferred to a separatory funnel, and washed successively with water (2 × 10 mL), 5% aqueous sodium bicarbonate and brine. The organic layer was dried over $MgSO_4$ and the solvent was evaporated to afford a colorless oil that was dissolved in THF (25 mL) and cooled on ice. $Ba(OH)_2$ (7.5 mL of 0.8 M aqueous solution) was added and the reaction was stirred at –10° C. After 16 h, the THF was evaporated and the residue was cooled to 0° C, carefully acidified and transferred to a separatory funnel. Ethyl acetate was added and the two

layers were separated. The aqueous layer was returned to the funnel and extracted with ethyl acetate. The desired carboxylic acid was recovered by extraction of the combined organic layer with 5% aqueous $NaHCO_3$ solution (3 × 10 mL), acidification of the combined aqueous layers with 10% aqueous HCl on ice and re-extraction with ethyl acetate. The organic layer was dried over magnesium sulfate and the solvent was removed to afford a 1:1 mixture of two epimers of **47** as a colorless oil (0.13 g, 83%). ^{1}H NMR (300 MHz, $CDCl_3$): 9.06-8.22 (bs, 2H), 6.13-6.03 (m, 1H), 6.02-6.91 (m, 2H), 5.90-5.82 (m, 1H), 4.84-4.79 (bs, 1H), 4.68-4.63 (m, 1H), 4.27-4.06 (m, 2H), 3.64 (dt, J = 3.1, 6.9 Hz, 1H), 3.23 (dt, J = 3.5, 7.3 Hz, 1H), 2.41-2.28 (m, 4H), 1.92-1.78 (m, 4H), 1.03 (t, J = 7.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.3, 173.0, 157.3, 157.0, 127.0, 126.1, 121.9, 121,5, 84.1, 83.6, 56.4, 54.9, 53.6, 52.9, 29.5, 28.8, 27.0, 26.1, 20.7, 9.2, 8.8; IR ($CHCl_3$ cast) ν_{max} = 3490-2250, 1748, 1529, 1427, 1394, 1330, 1305, 1241, 1197 cm^{-1}; HRMS (ES): *m/z*: calcd for $C_{10}H_{13}NO_4Na$: 234.0737; found: 234.07365 $[M+Na]^+$.

5.4.10 (-)-Methyl palustramate (1) and (-)-2-epi-methyl palustramate (2-epi-1)



1 C2-epi **1**

Compound **47** (100 mg, 0.46 mmol) was dissolved in CH_2Cl_2 (3 mL) and the solution was cooled on ice. DMF (5 µl) was added followed by oxalyl chloride (85 µl, 0.1 mmol) and the mixture was stirred for 15 min, brought to RT and stirred for 4h. The solvent was removed and the residue was stirred vigorously in ether (5 mL), then filtered. The filtrate

was added to an ice-cold solution of freshly prepared CH_2N_2 in ether (8-10 mmol). After 30 min, the reaction mixture was brought to RT and stirred for 20 h. The solvent was removed to afford a yellow oil, which was dissolved in methanol (10 mL) at 0° C. Silver benzoate (35 mg) and freshly distilled triethylamine (0.21 mL) were added sequentially and the resulting mixture was stirred at RT for 24 h in the exclusion of light. The reaction mixture was then filtered through Celite, the solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate and washed with 5% aqueous NaOH, brine. The organic layer was then dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in a 1:1 mixture of dimethoxyethane/water (8mL), $Ba(OH)_2$ (0.37 g, 2 mmol) was added and the reaction mixture was refluxed for 48 h. The solution was then cooled to RT and carbon dioxode was bubbled through the solution for 3-5 min. The white precipitates were removed by filtration. The solvent was evaporated to afford a white solid, which was dissolved in anhydrous methanol (1.5 mL) and cooled to –20° C. Thionyl chloride (0.08 ml) was carefully added and the reaction mixture was stirred at RT for 20 h. Methanol was removed and the residue was dissolved in dichloromethane and washed with aqueous $NaHCO_3$ and brine. The solvent was removed under vacuum to afford a black oil. The two diastereomers were separated by flash chromatography (4% $MeOH/CH_2Cl_2$) to afford **1** (26 mg) and its C2-epimer (27 mg).

Characterization data for 1

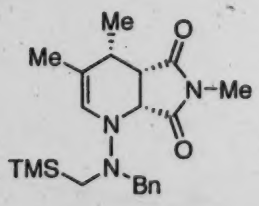
TLC (10%, $MeOH/CH_2Cl_2$, $KMnO_4$, PMA): 0.26; ^1H NMR (300 MHz, $CDCl_3$): δ = 5.87-5.79 (m, 1H), 5.61 (dm, J = 10.1 Hz, 1H), 3.82-3.77 (m, 1H), 3.70 (s, 3H), 3.30 (dt, J = 3.2, 8.6 Hz, 1H), 2.71 (ddd, J = 4.4, 8.0, 12.2 Hz, 1H), 2.50 (dd, J = 3.6,15.5 Hz, 2H),

2.08-1.82 (m, 2H), 1.62 (dp, J = 3.5, 7.3 Hz, 1H), 1.42 (sept, J = 7.3 Hz, 1H), 1.0 (t, J = 7.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2, 129.5, 126.4, 75.4, 57.3, 51.7, 51.5, 40.4, 27.8, 26.1, 9.6; HRMS (ES): m/z: calcd for $C_{11}H_{20}NO_3$: 214.1440; found: 214.1438 $[M+H]^+$; $[\alpha]_D^{23}$ = -19.4 (c = .18 in CH_2Cl_2); litt.: ($[\alpha]_D^{23}$ = -18.2 (c = 0.0044 in CH_2Cl_2)

Characterization data for C2-epi 1

TLC (10%, MeOH/CH_2Cl_2, $KMnO_4$, PMA): 0.19; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.87-5.82 (m, 1H), 5.76 (dm, J = 10.1 Hz, 1H), 3.92-3.86 (m, 1H), 3.70 (s, 3H), 3.26 (dt, J = 3.2, 8.1 Hz, 1H), 2.69 (ddd, J = 4.4, 8.4, 12.4 Hz, 1H), 2.54 (dd, J = 9.5, 15.1 Hz, 1H), 2.46 (dd, J = 5.1, 15.0 Hz, 1H), 2.05 (dm, J = 17.4 Hz, 1H), 1.99-1.42 (bs, 2H), 1.83 (ddq, J = 2.4, 6.2, 10.5 Hz, 1H), 1.62-1.56 (m, 1H), 1.40 (app sept, J = 7.5 Hz, 1H), 1.0 (t, J = 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3, 129.4, 126.1, 74.7, 52.0, 51.7, 49.6, 39.2, 27.3, 26.1, 9.7; IR (CH_2Cl_2 cast) ν_{max} = 3324, 3028, 2959, 2922, 1735, 1436, 1351, 1273 cm^{-1}; HRMS (ES): m/z: calcd for $C_{11}H_{20}NO_3$: 214.1440; found: 214.1438 $[M+H]^+$; $[\alpha]_D^{23}$ = -53.2 (c = 0.64 in CH_2Cl_2).

5.4.11 Rac-(*2aR,5R,6aS*)-3-[(trimethylsilylmethyl)benzylamino]-1,4,5-trimethyl-(3a,4,6,6a)-tetrahydrooxazolo[3,4-a]pyridin-2,8 (1H)-dione (51)

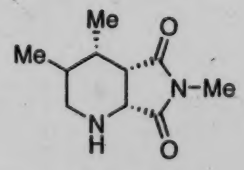


3-Methyl-2-butenal (0.11 mL, 1.2 mmol) was added to a solution of hydrazine **34** (0.24 g, 1.2 mmol) in CH_2Cl_2 (8 mL) at RT. Magnesium sulfate (1.3 equiv) was added and the

resulting mixture was refluxed for 2 h, cooled to RT and filtered. The filtrate was evaporated and the residue was dissolved in acetonitrile (12 mL). *N*-methyl maleimide (0.146 g, 1.32 mmol) was added and the resulting mixture was heated at 50° C for 16 h. The solvent was evaporated and the residue was purified by flash chromatography to afford the product **51** as a colorless oil (0.28 g, 67%).

TLC (20%, EtOAc/hexane, $KMnO_4$, PMA): 0.42; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40-7.21 (m, 5H), 6.05 (s, 1H), 4.04 (d, J = 5.4 Hz, 1H), 3.91 (d, J = 13.2 Hz, 1H), 3.87 (d, J = 13.2 Hz, 1H), 3.50 (d, J = 4.0 Hz, 1H), 2.98 (s, 3H), 2.68-2.62 (m, 1H), 2.46-2.40 (m, 2H), 2.32 (d, J = 14.1 Hz, 1H), 1.65 (s, 3H), 0.70 (d, J = 7.1 Hz, 3H), 0.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.2, 176.7, 138.6, 129.2, 128.2, 128.1, 128.0, 127.1, 108.9, 60.8, 41.5, 32.2, 23.8, 18.7, 13.8, -1.6; IR ($CHCl_3$ cast) ν_{max} = 3479, 3062, 3029, 2959, 2897, 1783, 1712, 1603, 1495, 1453, 1431, 1379, 1247 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{21}H_{31}N_3O_2Si$: 385.2186; found: 385.2181 $[M]^+$.

5.4.12 Rac-(*2aR,4epi-5S,6aS*)-1,4,5-trimethylhexahydrooxazolo[3,4-a]pyridin-2,8 (1H)-dione (53).



Product **51** (55 mg, 0.14 mmol) was dissolved in methanol (3 mL), and to this solution were added sodium cyanoborohydride (18 mg, 0.29 mmol) and anhydrous zinc chloride (25 mg, 0.14 mmol) in that order. The reaction mixture was stirred at room temperature for 5 h and the solvent was evaporated. The residue was dissolved in ethyl acetate and

washed with aqueous $NaHCO_3$ solution and brine, then dried over magnesium sulfate. The solvent was evaporated and the residue was purified by flash chromatography using a 6:1 hexane: ethyl acetate solvent mixture to afford the product as a 2:1 mixture of diastereomers (49 mg, 92%). This mixture (35 mg, 0.09 mmol) was dissolved in ethanol 95% (3 ml) and 10% aqueous HCl (0.31 mL) was added at room temperature. The resulting solution was heated to 50° C for 20 h, then cooled to room temperature. The solvent was evaporated under reduced pressure, the residue cooled on ice and treated with 5% aqueous $NaHCO_3$. Ethyl acetate was added and the biphasic mixture was transferred to a separatory funnel. The two layers were separated and the aqueous phase was further extracted with ethyl acetate. The combined organic layers was washed with brine, then dried over magnesium sulfate. The residue was purified on silica gel using 3% MeOH in CH_2Cl_2 to afford the major diastereomer (11 mg) and the minor one (5 mg).

TLC (5%, MeOH/CH_2Cl_2, $KMnO_4$, PMA): 0.27; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.79 (d, J = 7.6 Hz, 1H), 2.98 (s, 3H), 3.02-2.97 (m, 1H), 2.78 (dd, J = 5.5, 12.2 Hz, 1H), 2.58 (dd, J = 9.0, 12.0 Hz, 1H), 2.34-2.23 (m, 1H), 1.84-1.74 (m, 1H), 1.36-1.23 (m, 1H), 0.91 (d, J = 7.4 Hz, 3H), 0.89 (d, J = 7.0 Hz, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ =178.7, 177.9, 54.3, 45.3, 44.2, 32.5, 24.2, 15.9, 10.6; IR ($CHCl_3$ cast) ν_{max} = 3323, 2964, 1777, 1708, 1530, 1434, 1383, 1275 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{10}H_{16}N_2O_2$: 196.1212; found: 196.1210 $[M]^+$.

5.5 References and notes

(1) Chandrasekhar, S.; Reddy, C. R.; Rao, R. J. *Synlett* **2001**, 1561-1562.

(2) Clive, D. L. J.; Zhang, J.; Subedi, R.; Bouetard, V.; Hiebert, S.; Ewanuk, R. *J. Org. Chem.* **2001**, *66*, 1233-1241.

(3) Kim, Y. H.; Choi, J. Y. *Tetrahedron Lett.* **1996**, 5543-5546.

(4) Genari, C.; Colombo, L.; Bertolini, G.; *J. Am. Chem. Soc.* **1986**, *108*, 6394-6395.

(5) Claremon, D. A.; Lumma, P. K.; Plillips, B. T. *J. Am. Chem. Soc.* **1986**, *108*, 8265-8266.

(6) Perz Luna, A.; Ceschi, M. –A.; Bonin, M.; Micouin, L; Husson, H. –P.; Gougeon, S.; Estenne-Bouhtou, G.; Marabou, B.; Sevrin, M.; George, P.; *J. Org. Chem.* **2002**, *67*, 3522-3524.

(7) Hinman, R. L.; *J. Org. Chem.* **1957**, *22*, 148-150.

(8) Enders, D.; Schubert, H.; Nubling, C. *Angew. Chem. Int. Ed.* **1986**, *25*, 1109-1110.

(9) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 6397-6399.

(10) Feuer, H.; Brown, F., Jr. *J. Org. Chem.* **1970**, *35*, 1468-1471.

(11) Enders, D.; Lochtman, R.; Meiers, M.; Muller, S.; Lazny, R. *Synlett* **1998**, 1182-1184.

(12) Sturino, C. F.; Fallis, A. G. *J. Am. Chem. Soc.* **1994**, *116*, 7447-7448.

(13) Mellors, J. M.; Smith, N. M. *J. Chem. Soc., Perkin Trans. 1*, **1984**, *96*, 2927-2931.

(14) Denmark, S. E.; Nicaise, O.; Edwards, J. P. *J. Org. Chem.* **1990**, *55*, 6219-6323.

(15) Enders, D.; Tiebes, J.; De Kimpe, N.; Keppens, M.; Stevens, C.; Smagghe, G.; Bertz, O. *J. Org. Chem.* **1993**, *58*, 4881-4184.

(16) Souppe, J.; Danon, L.; Namy, J. L.; Kagan, H. B. *J. Organomet. Chem.* **1983**, *250*, 227-236.

(17) Burk, M. J.; Feaster, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 6266-6267.

(18) Ding, H.; Friestad, G. K. *Org. Lett.* **2004**, *6*, 637-640.

(19) Fernández, R.; Ferrete, A.; Lassaletta, J. M.; Llera, J. M.; Monge, A. *Angew. Chem.* **2000**, *112*, 3015; *Angew. Chem. Int. Ed.* **2000**, *39*, 2893-2897.

(20) Fernández, R.; Ferrete, A.; Lassaletta, J. M.; Llera, J. M.; Martin-Zamora, E. *Angew. Chem. Int. Ed.* **2002**, *41*, 831-833.

(21) For a review see: Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron* **2002**, *58*, 2253.

(22) See Chapter 2 of this thesis for the preparation of diene **9**.

(23) Olofson, R. A.; Schnur, R. C.; Bunes, L.; Pepe, J. P. *Tetrahedron Lett.* **1977**, 1567-1570.

(24) Olofson, R. A.; Martz, J. T.; Senet, J. P.; Piteau, M.; Malfoot, T. *J. Org. Chem.* **1984**, *49*, 2081-2082.

(25) Yang, B. V.; O'Rourke, D.; Li, J. *Synlett* **1993**, 195-196.

(26) Serckx-Poncin, B.; Hesbain-Frisque, A. -M.; Ghosez, L. *Tetrahedron Lett.* **1982**, *32*, 3261-3264.

(27) See the supporting information for the preparation compound **1** in: Buckmelter, A. J.; Kim, A. I; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2000**, *122*, 9386-9390.

(28) Lipshutz, B. H.; Pegram, J. J. *Tetrahedron Lett.* **1980**, *21*, 3343-3346.

(29) Matthews, D. P.; McCarthy J. R. *J. Org. Chem.* **1986**, *51*, 1891-1894.

(30) Legault, C.; Charette A. B. *J. Org. Chem.* **2003**, 7119-7122.

(31) (a) Haga, N.; Endo, Y.; Kataoka, K.-I.; Yamaguchi, K.; Shudo, K. *J. Am. Chem. Soc.* **1992**, *114*, 9795-9801. (b) Carpino. L. A.; Giza, C. A.; Carpino, B. A. *J. Am. Chem. Soc.* **1959**, 955-957.

(32) Washizuka, K. –I.; Nagai, K.; Minakata, S.; Ryu, I.; Komatsu, M. *Tetrahedron Lett.* **1999**, *40*, 8849-8853.

(33) White, E. M. *J. Am. Chem. Soc.* **1955**, *48*, 2424-2426. (b) Evans, D. A.; Carter, P. H.; Dinsmore, C. J.; Barrow, J. C.; Katz, J. L.; Kung, D. W. *Tetrahedron Lett.* **1997**, *38*, 4535-4538.

(34) Evans, D. A.; Carter, P. H.; Dinsmore, C. J.; Barrow, J. C.; Katz, J. L.; Kung, D. W. *Tetrahedron Lett.* **1997**, *38*, 4535-4538

(35) Bailey, T. R.; Garigipati, R. S.; Morton, J. A.; Weinreb, S. M. *J. Am. Chem. Soc.* **1984**, *106*, 3240-3245.

(36) Angle, S. R.; Henry, R. M. *J. Org. Chem.* **1998**, *63*, 7490-7497.

(37) The preparation of this class of compounds was discussed in Chapter 2 of this thesis.

(38) Tailor, J. *M.Sc. thesis*, University of Alberta, Edmonton, Alberta 2000.

(39) Touré, B. B.; Hoveyda, H. R.; Tailor, J.; Ulaczyk-Lesanko, A.; Hall, D .G. *Chem. Eur. J.* **2003**, *9*, 466-474.

Thesis Conclusions

This thesis has described the development of new organoboron methodologies aimed at rapidly assembling polysubstituted piperidine derivatives and their subsequent applications to the diversity-oriented synthesis of α-hydroxyalkyl piperidines, as well as the asymmetric synthesis of palustrine alkaloids. Our interest in these alkaloids was piqued by the presence of an α-hydroxyalkyl piperidine motif, and the important biological activity endowed in some natural products harboring the latter unit. Indeed, the stereoselective construction of the α-hydroxyalkyl piperidine unit represents a significant synthetic challenge. Our approach to these compounds featured a highly convergent three-component aza[4+2]cycloaddition/allylboration/retro-sulfinyl-ene reaction.

The success of our strategy hinged on the development of a convenient synthetic route to 1-amino-1-aza-4-boronopinacolate butadienes, which represent key components of the above-mentioned multicomponent reaction. These efforts culminated with the development of a convenient procedure for the isolation of functionalized *E*-1-alkenylboronic acids including the important 3-boronoacrolein intermediate. These compounds are notoriously difficult to handle and to purify, thus our contribution in this area, although mainly technical, can be regarded as important. This process is currently used by many members of our laboratory and is certainly bound to find other applications in the literature.

With this improved procedure in hand, we next sought to increase the reactivity of the dienes via modulation of the electron density around the boron center. Studies aimed

at elucidating the scope and limitations of the aza[4+2]cycloaddition/allylboration three-component reaction were also initiated. This work clearly established that the reaction was indeed very general with regards to hydrazine and aldehyde components. All our attempts, however, to expand the reaction scope with respect to the dienophile component were unsuccessful. At this stage, the scope of the reaction appeared to be limited to diversity-oriented synthesis applications.

Despite this shortcoming, we reasoned that it may be possible to apply this methodology to the synthesis of the palustrine family of alkaloids if a suitable diactivated dienophile, bearing a sacrificial activating group, could be identified. This simply stated objective certainly did not entail stereoselectivity and regioselectivity issues, all-important for the synthesis of our targets. Efforts towards this goal led to the development of a highly regio and steroselective variant of the three-component aza[4+2]/allylboration, whereby maleimide was efficiently replaced with homochiral isothiazolidinone dienophiles. Very few MCRs display such a high level of regio and stereocontrol in the formation of highly functionalized nitrogen heterocycles. The products of this new MCR provided us with the opportunity to implement a regioselective desulfurization strategy concomitant with a necessary alkene migration. This work provided the first detailed retro-sulfinyl-ene reaction procedure. It also constituted the first example of a retro-sulfinyl-ene reaction in a heterocyclic context. A concise synthesis of (-)-methyl dihydropalustramate, the shortest sequence to date, was completed using this methodology. It is also noteworthy that the retro-sulfinyl-ene reaction had never been applied in a total synthesis effort prior to this work.

In order to apply this methodology to the synthesis of (-)-methyl palustramate, a chemoselective hydrazine cleavage process that preserves the integrity of double bonds had to be developed. This work resulted in the development of a new class of tetraalkylhydrazines, namely the *N*-(trimethylsilylmethyl)-*N*-benzyl hydrazines, which can be cleaved in the presence of double bonds under mildly acidic conditions. The asymmetric synthesis of the natural product (-)-methyl palustramate was completed using this pivotal methodology. A preliminary mechanistic study indicated that the proximal hydroxyl group accelerates the cleavage of the hydrazine moiety but is not essential necessary for the reaction to occur.

This chemoselective cleavage of tetraalkylhydrazines in the presence of unsaturations represents one of the most significant results to come from this thesis. This result opens up a whole new area of investigations and many exciting new applications can be envisioned. For example, the asymmetric synthesis of amines via the Diels-Alder reaction or the nucleophilic addition of organometallic intermediates onto imines is currently a very intense area of research. A chiral variant of our silylated hydrazines could find many interesting applications in this area.

During these studies, we have also gained insights into the conformations of 1,2,6-trisubstituted piperidines. For instance, some of our results suggest that these systems prefer to keep the 2,6-substituents in a diaxial orientation in order to accommodate the steric bulk at the 1-position. *Work on other related systems could further build on this interesting fundamental result.*

Overall, many significant fundamental and practical contributions have emerged from this thesis work, and it is expected that many methodologies developed herein will prove useful to the synthetic community.

Appendices

Representative ^{1}H and ^{13}C Spectra

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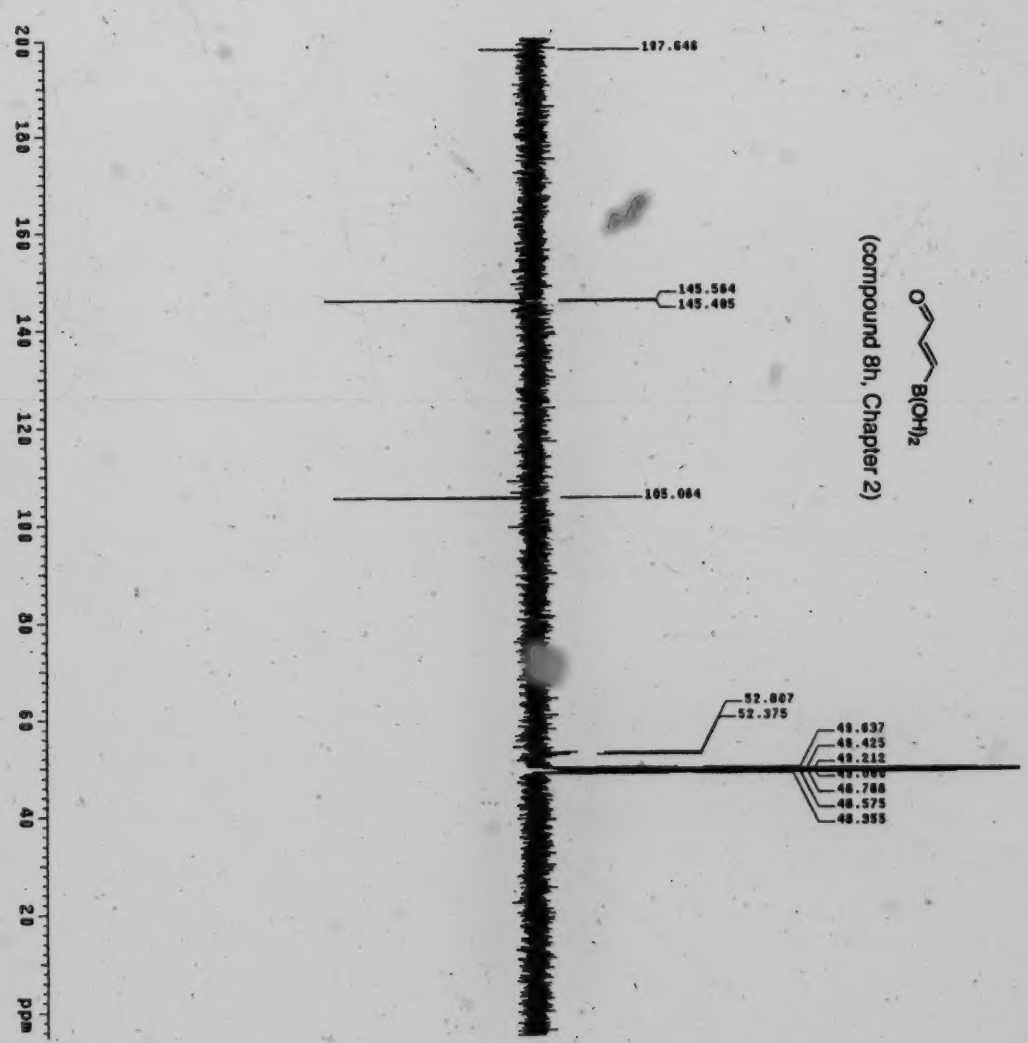
Appendix A

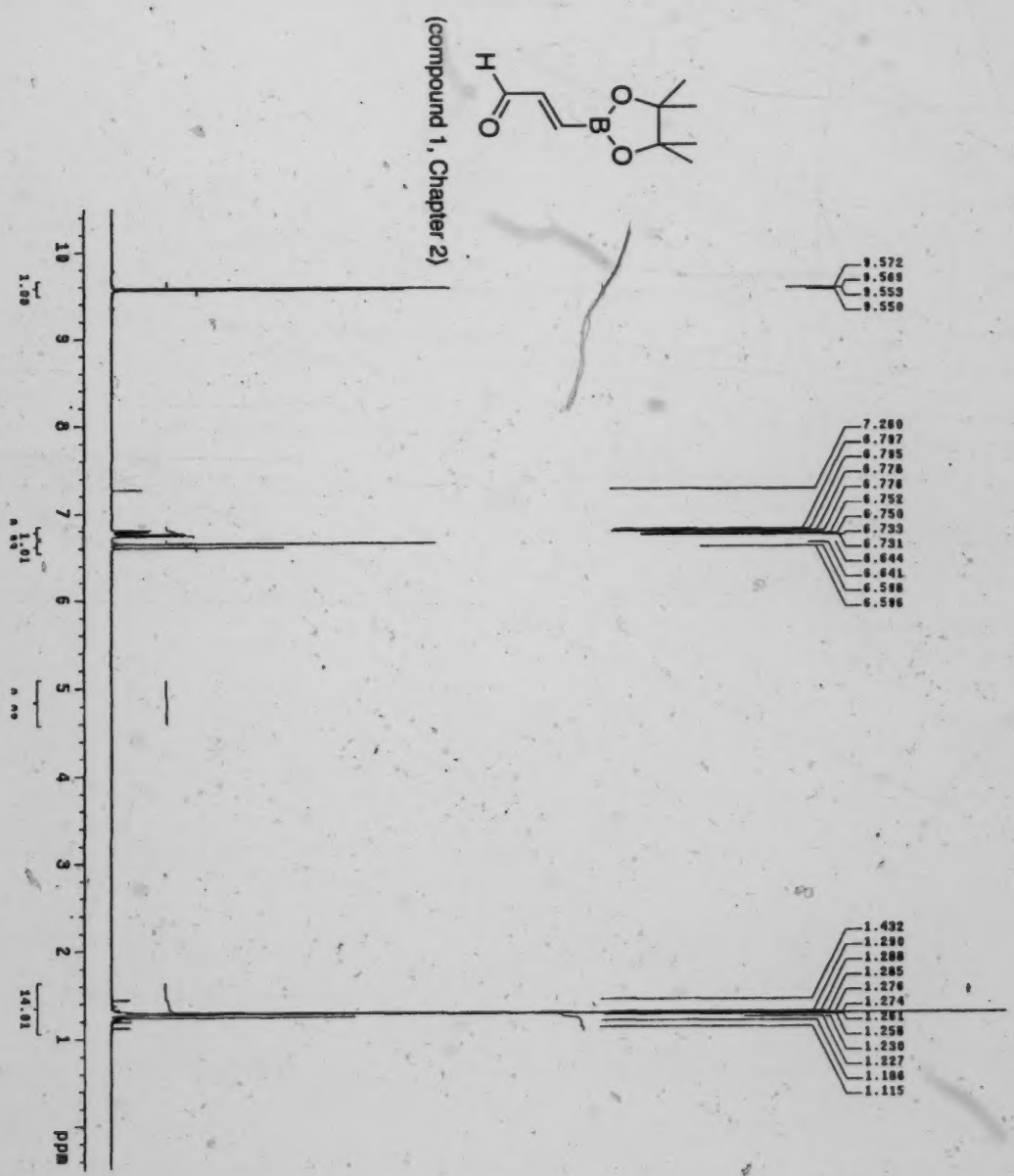
Representative ^{1}H NMR and APT spectra of *E*-1-alkenylboronic acids

These compounds were always observed as a mixture of boronic acids and anhydrides in different ratio.

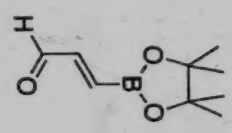

197.646
145.584
145.405
105.064
52.807
52.375
48.637
48.425
48.212
48.768
48.575
48.355
O
B(OH)2
(compound 8h, Chapter 2)
200
180
160
140
120
100
80
60
40
20
ppm

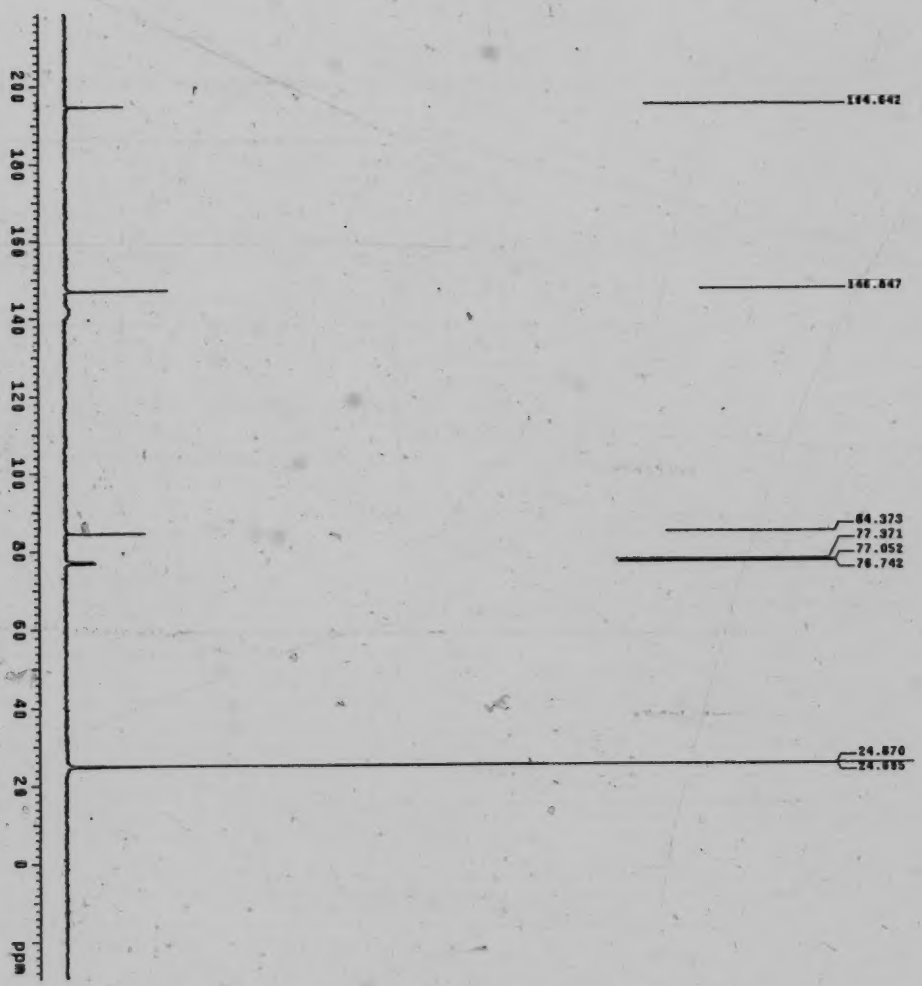
Appendix B

^{1}H NMR and APT spectra of 3-boronoacrolein pinacolate



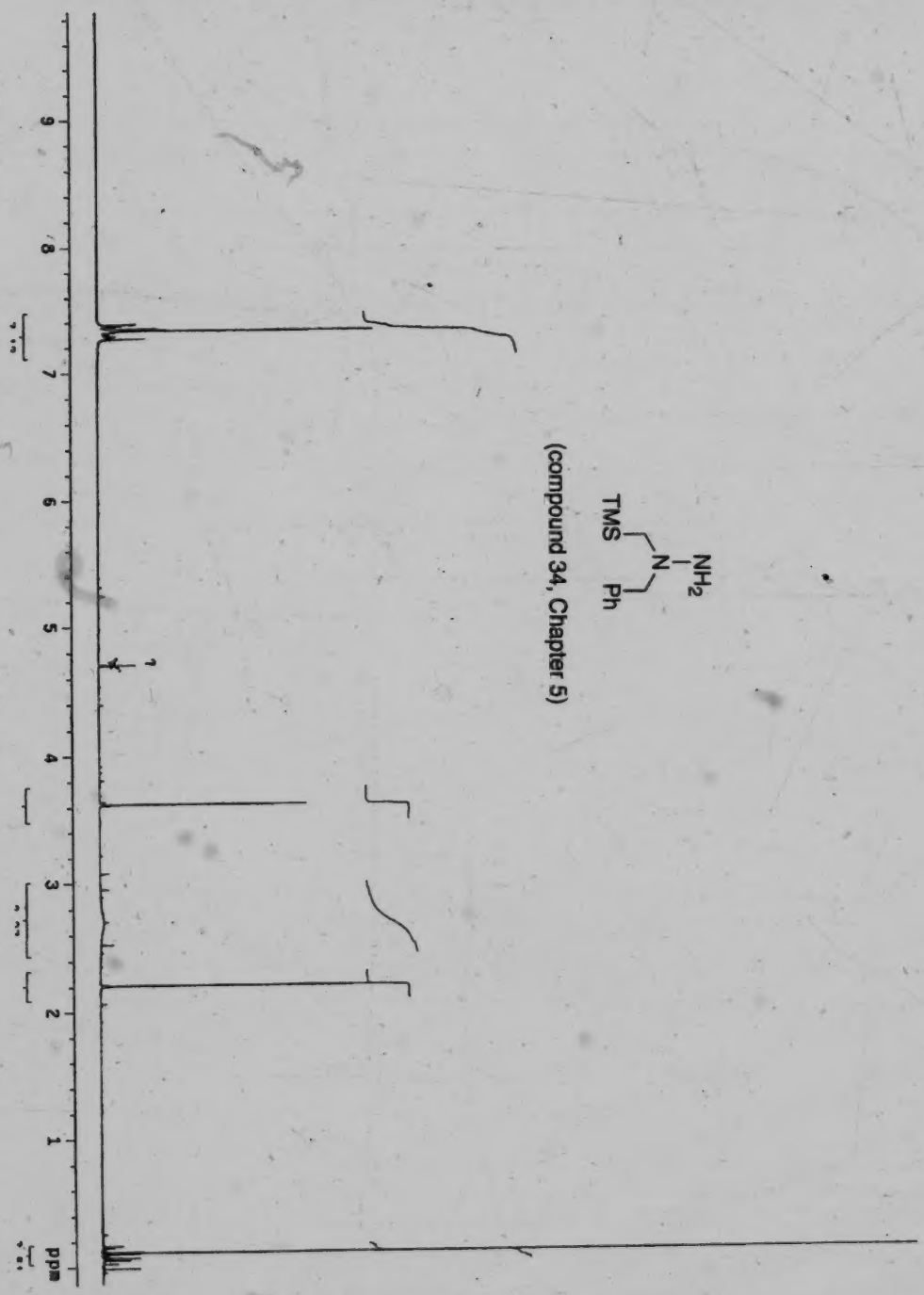
(compound 1, Chapter 2)

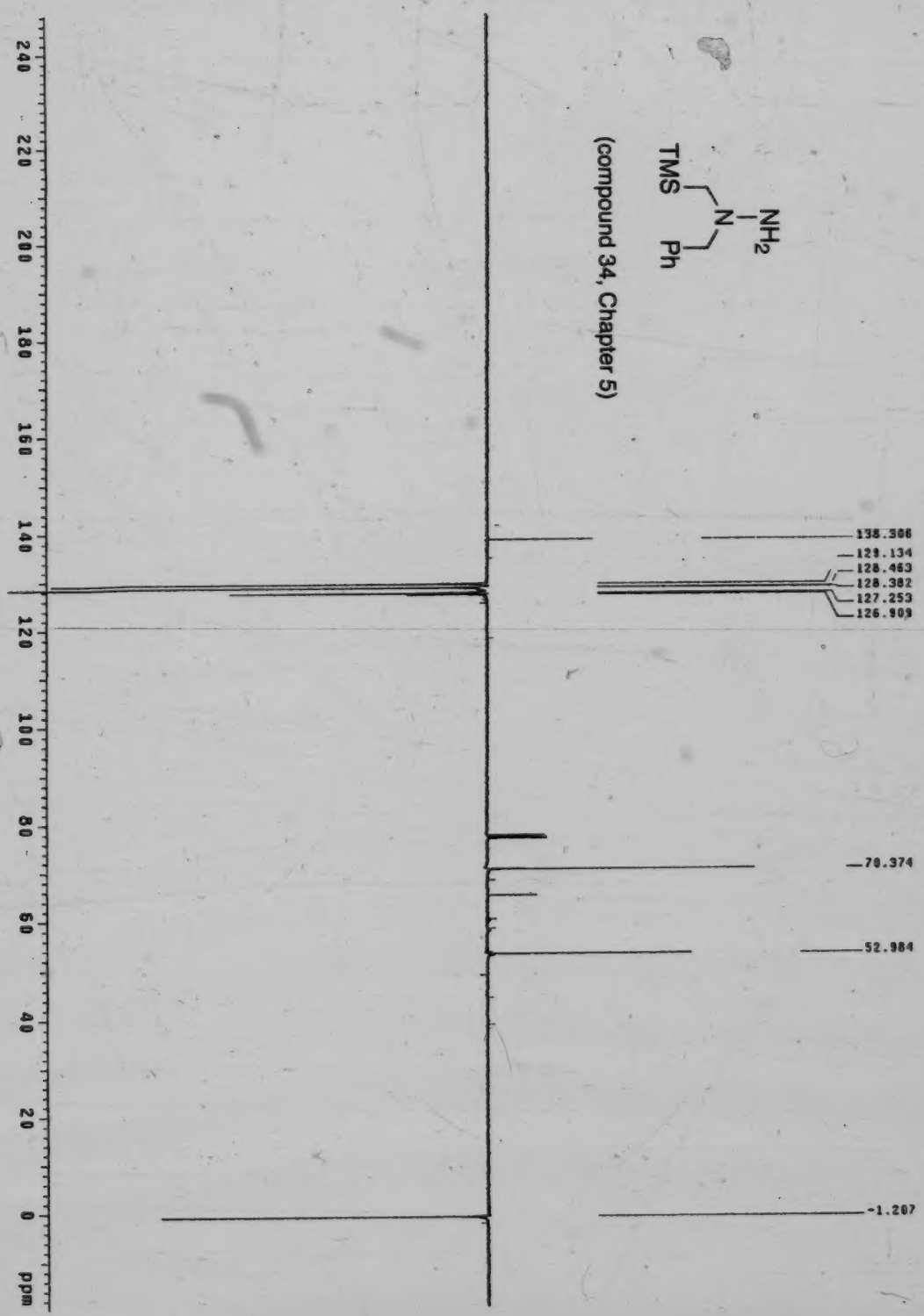




Appendix C

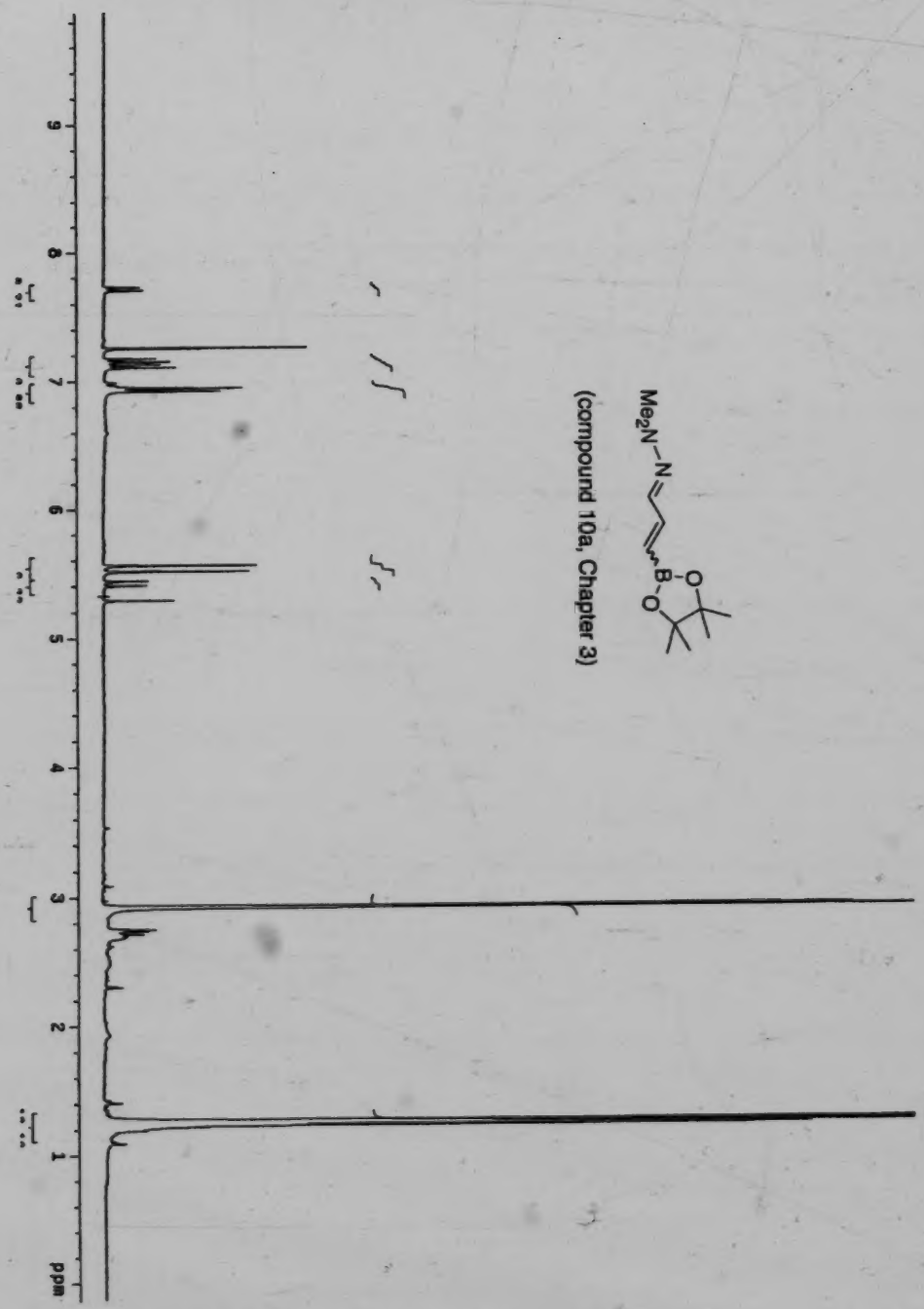
^{1}H NMR and APT spectra of (trimethylsilylmethyl)benzyl hydrazine



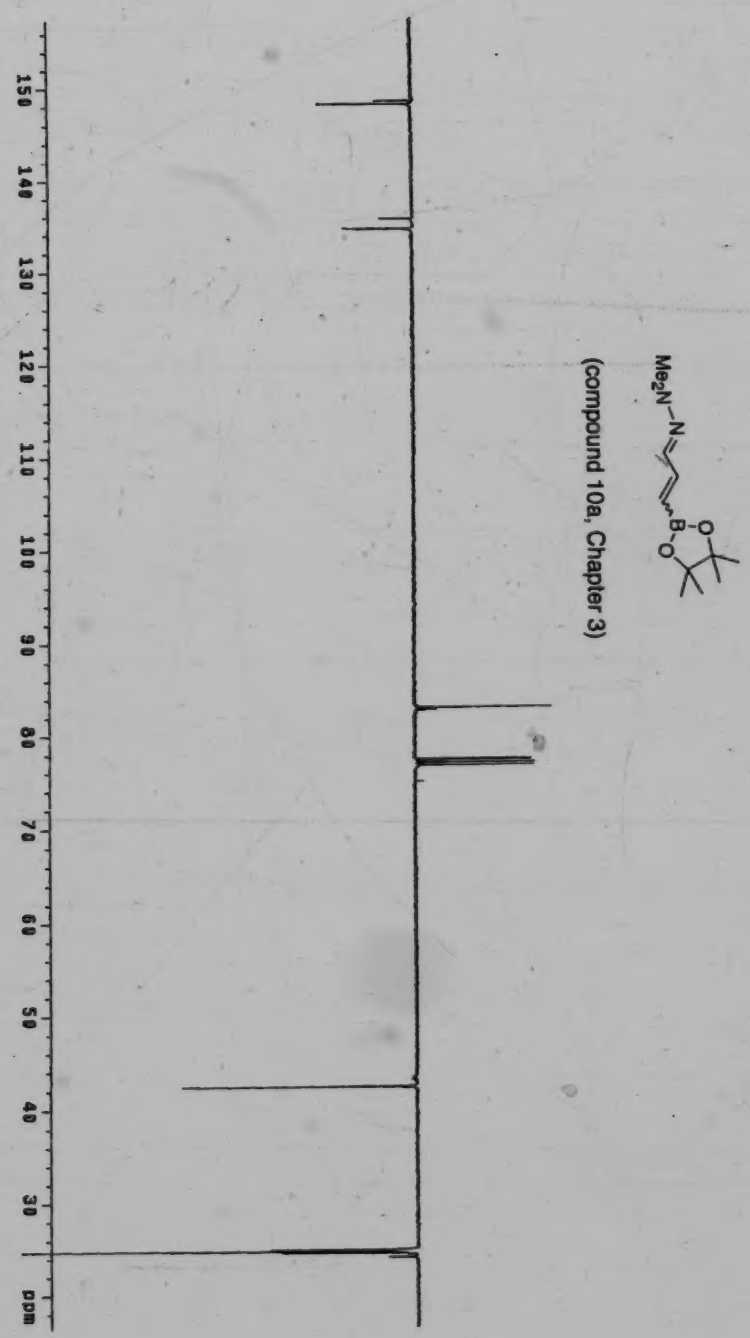

TMS
N
NH2
Ph
(compound 34, Chapter 5)
138.306
129.134
128.463
128.382
127.253
126.909
70.374
52.984
-1.207
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

Appendix D

Representative ^{1}H NMR and APT spectra of the dienes



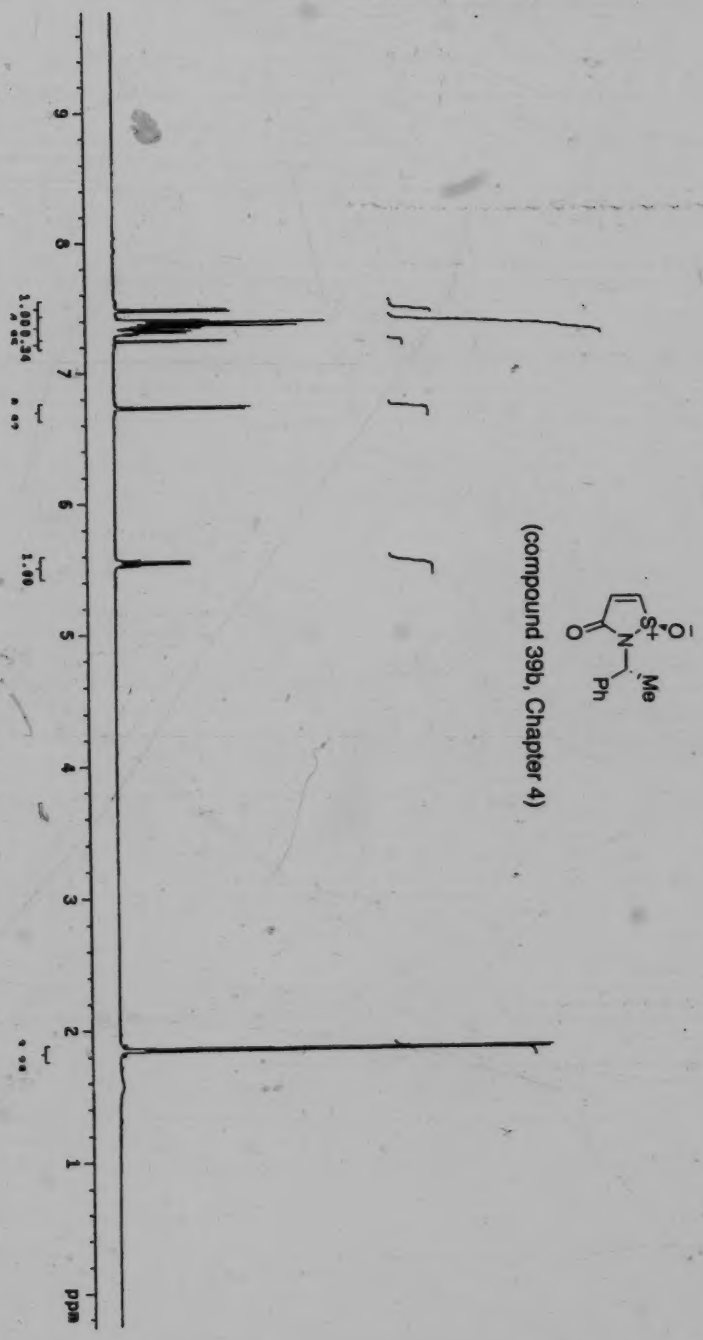
An unidentified impurity peak at 2.7 ppm is obseverved.

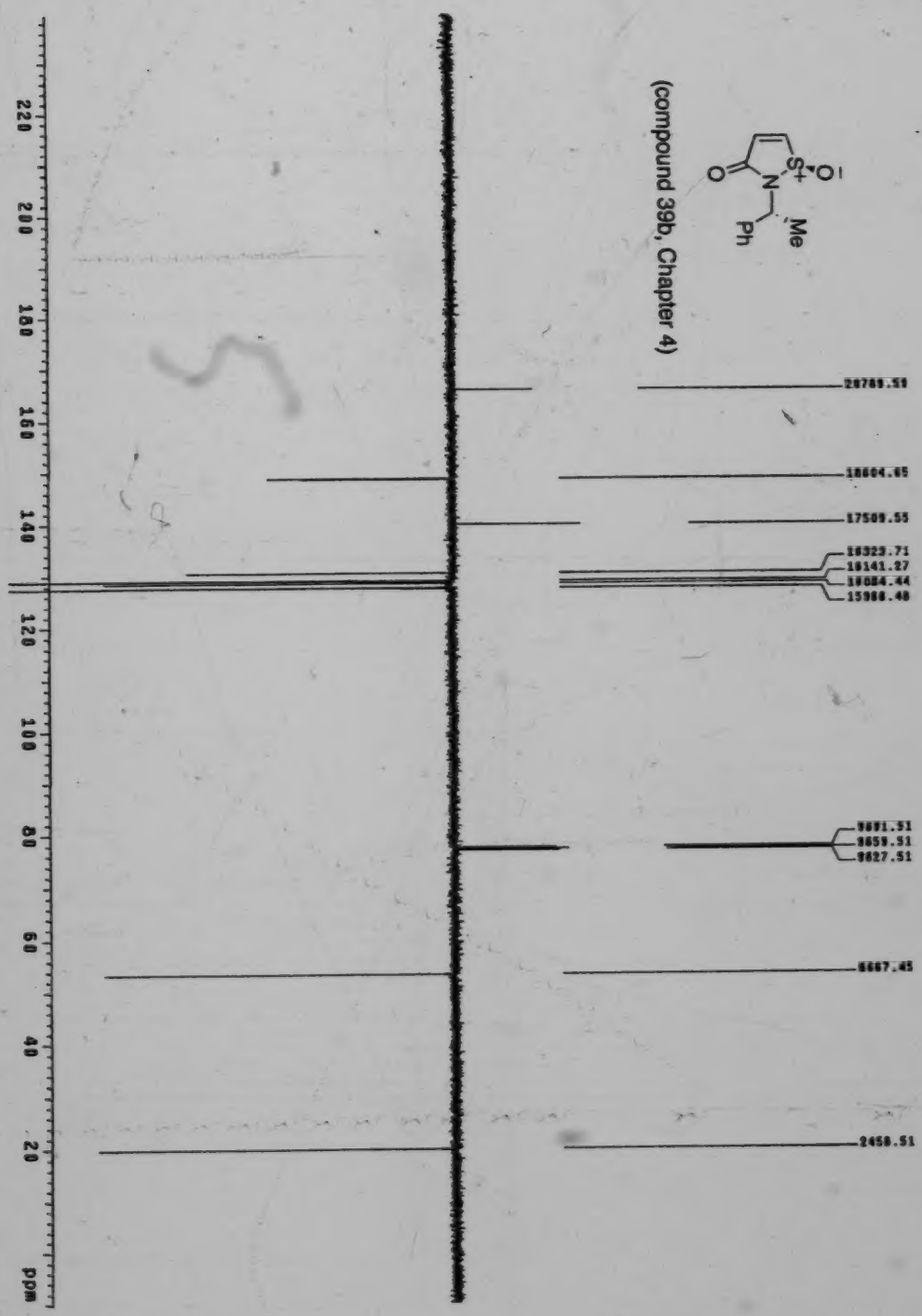


(compound 10a, Chapter 3)

Appendix E

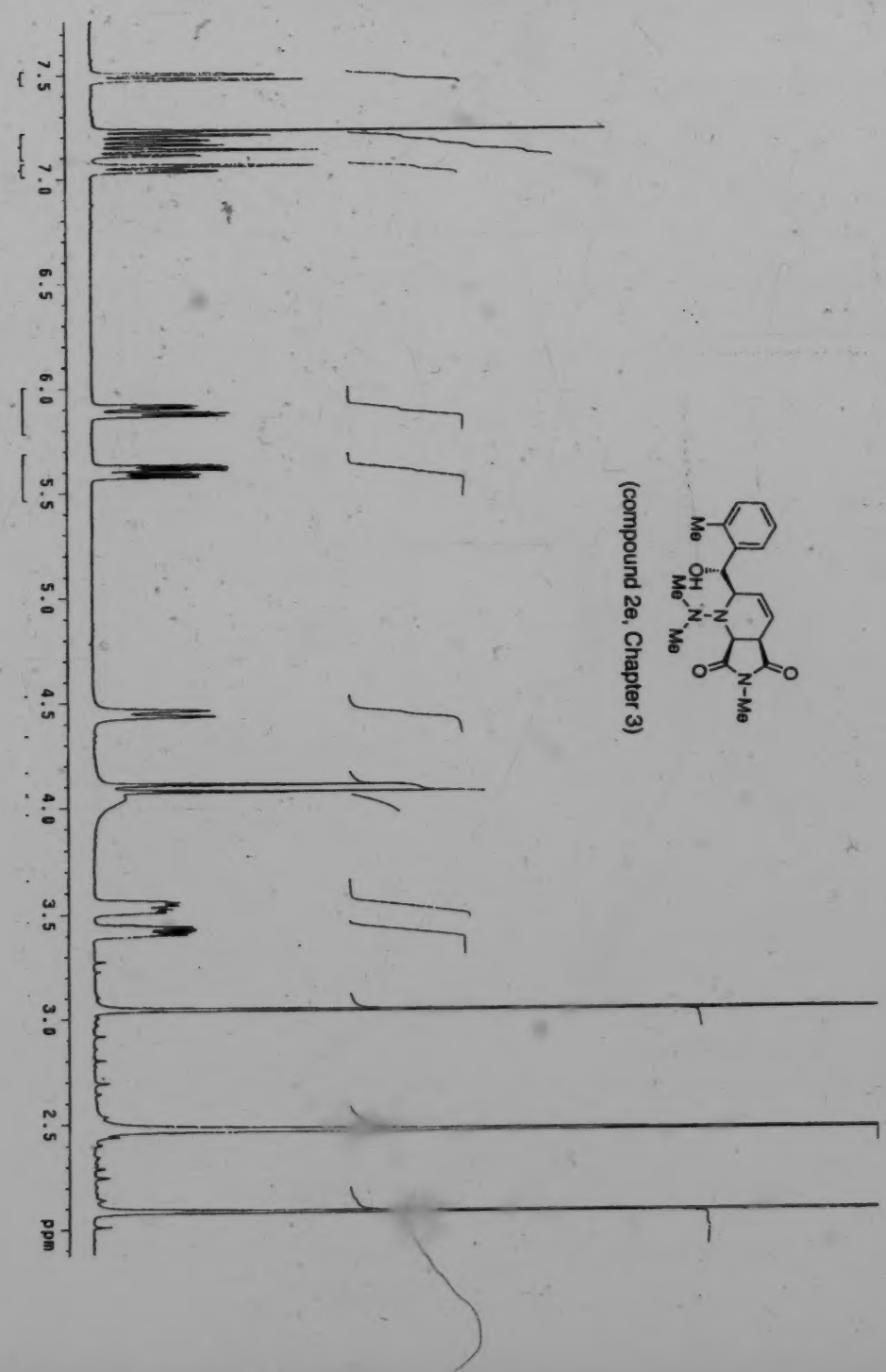
Representative ^{1}H NMR and APT spectra of the dienophiles

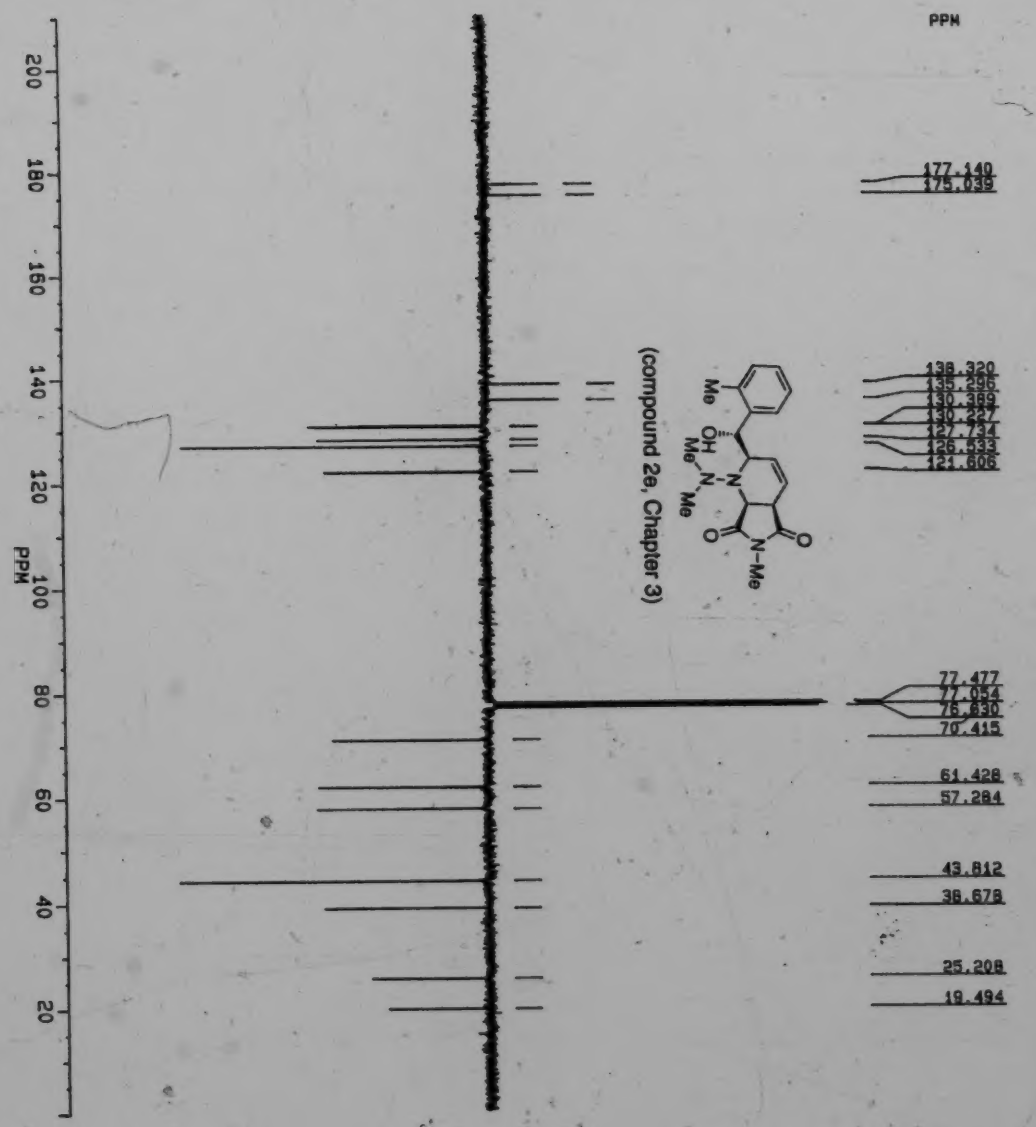


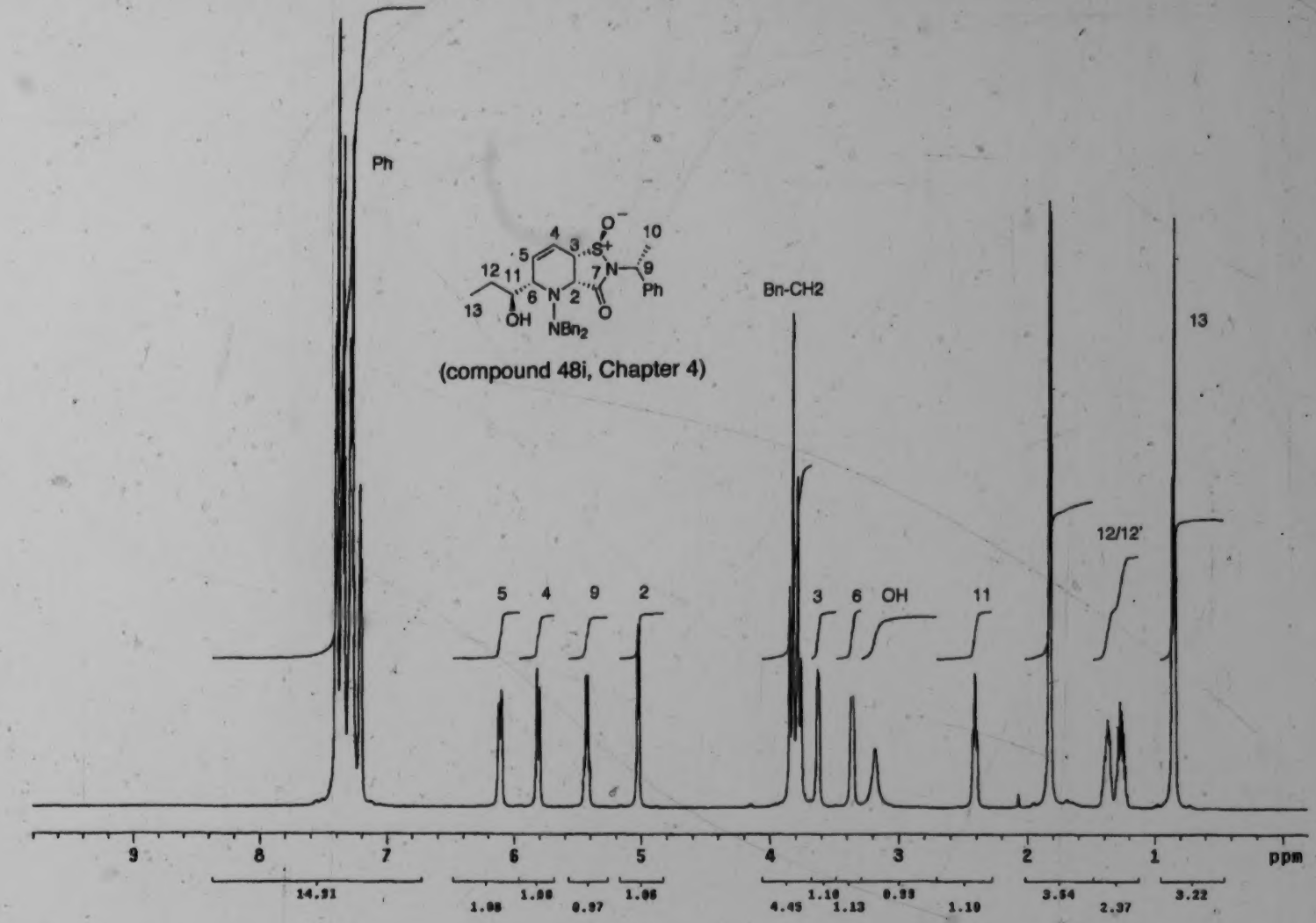

(compound 39b, Chapter 4)
Me
Ph
220
200
180
160
140
120
100
80
60
40
20
ppm
20785.51
18804.65
17509.55
16323.71
16141.27
16084.44
15988.48
9891.51
9859.51
9827.51
6667.45
2458.51

Appendix F

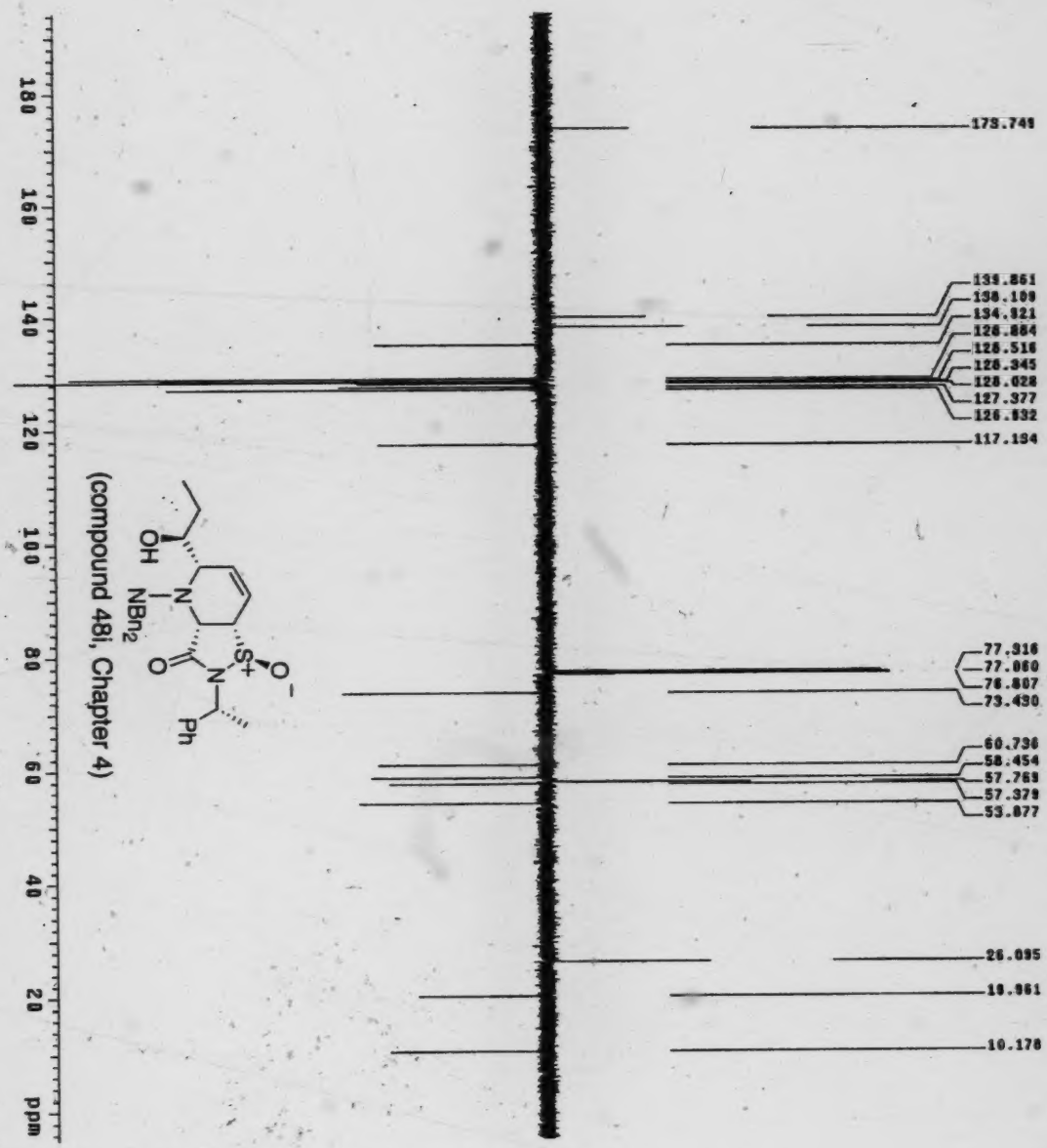
Representative ^{1}H NMR and APT spectra of the tandem aza[4+2]/allylboration reaction products



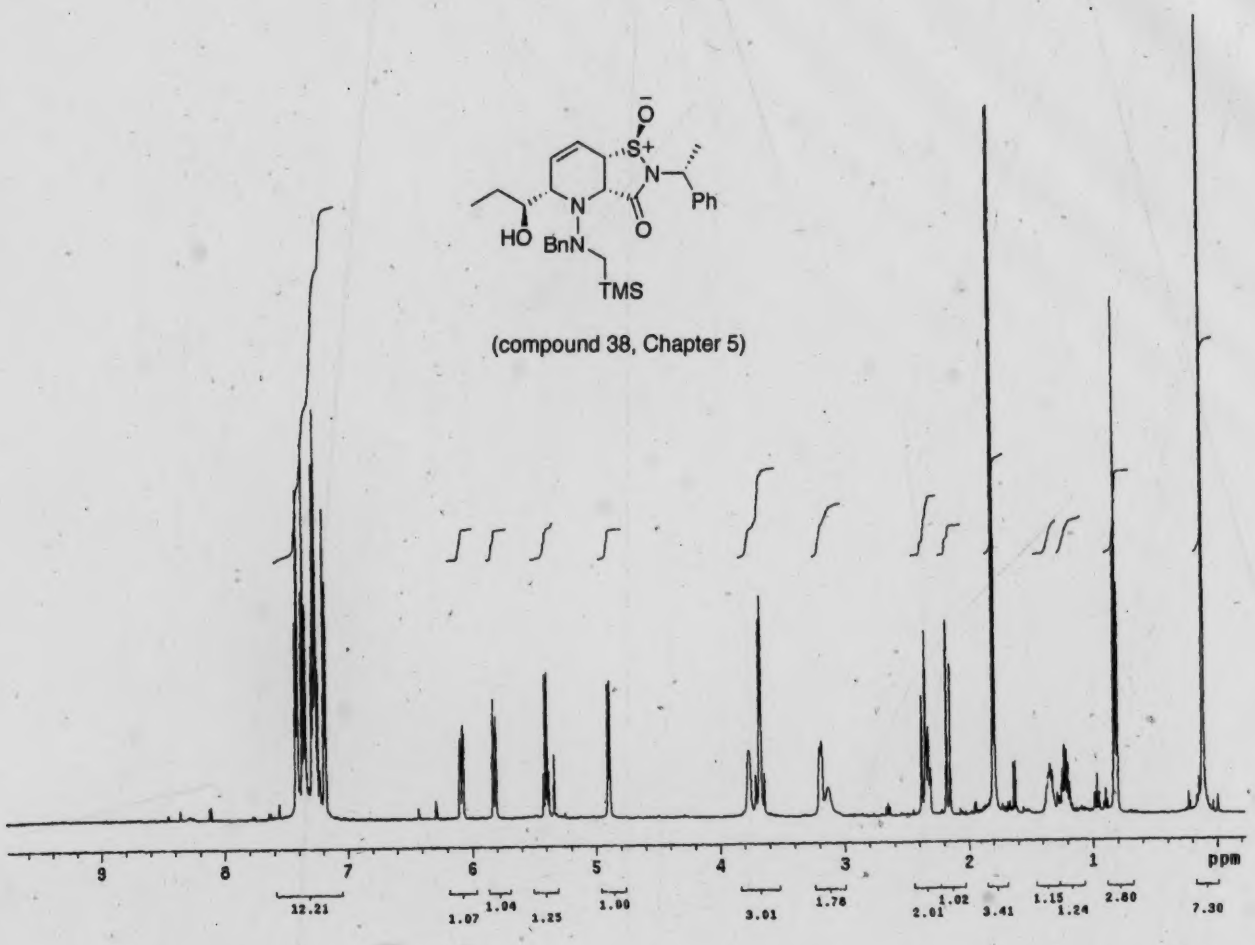

PPM
177.140
175.039
138.320
135.296
130.369
130.227
127.734
126.633
121.606
77.477
77.054
76.630
70.415
61.428
57.284
43.812
38.678
25.208
19.494
200
180
160
140
120
100
80
60
40
20
PPM
(compound 2e, Chapter 3)
Me
OH
Me
N
N
Me
O
O
N-Me



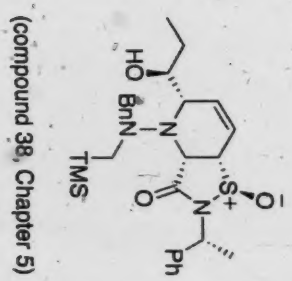
(compound 48i, Chapter 4)



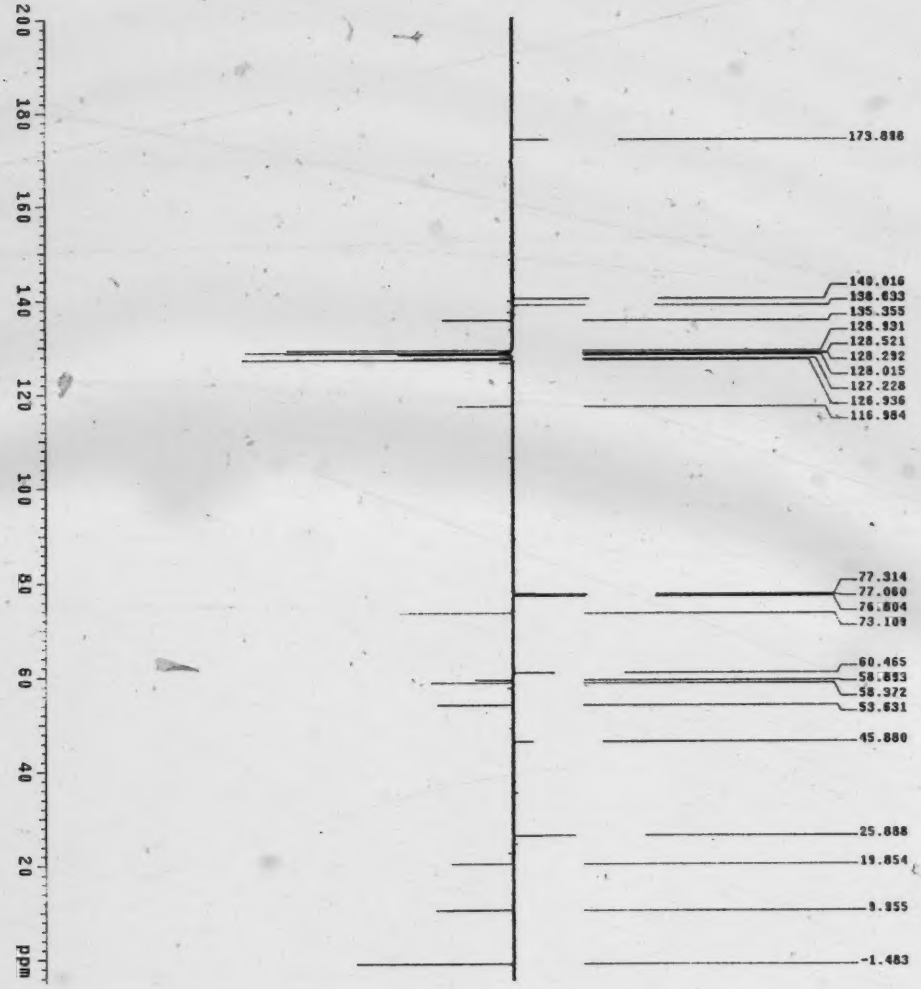
(compound 48i, Chapter 4)



(compound 38, Chapter 5)

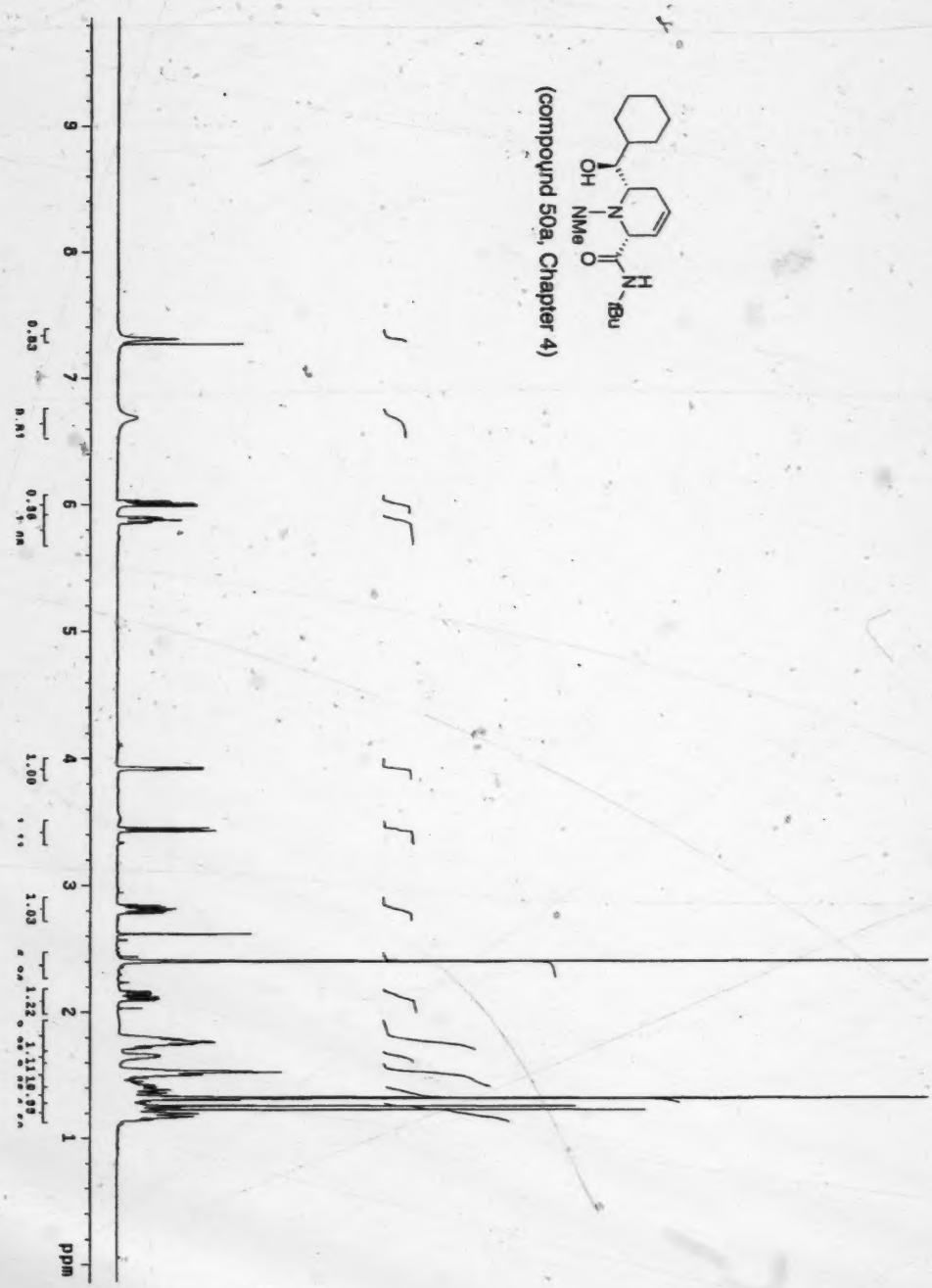


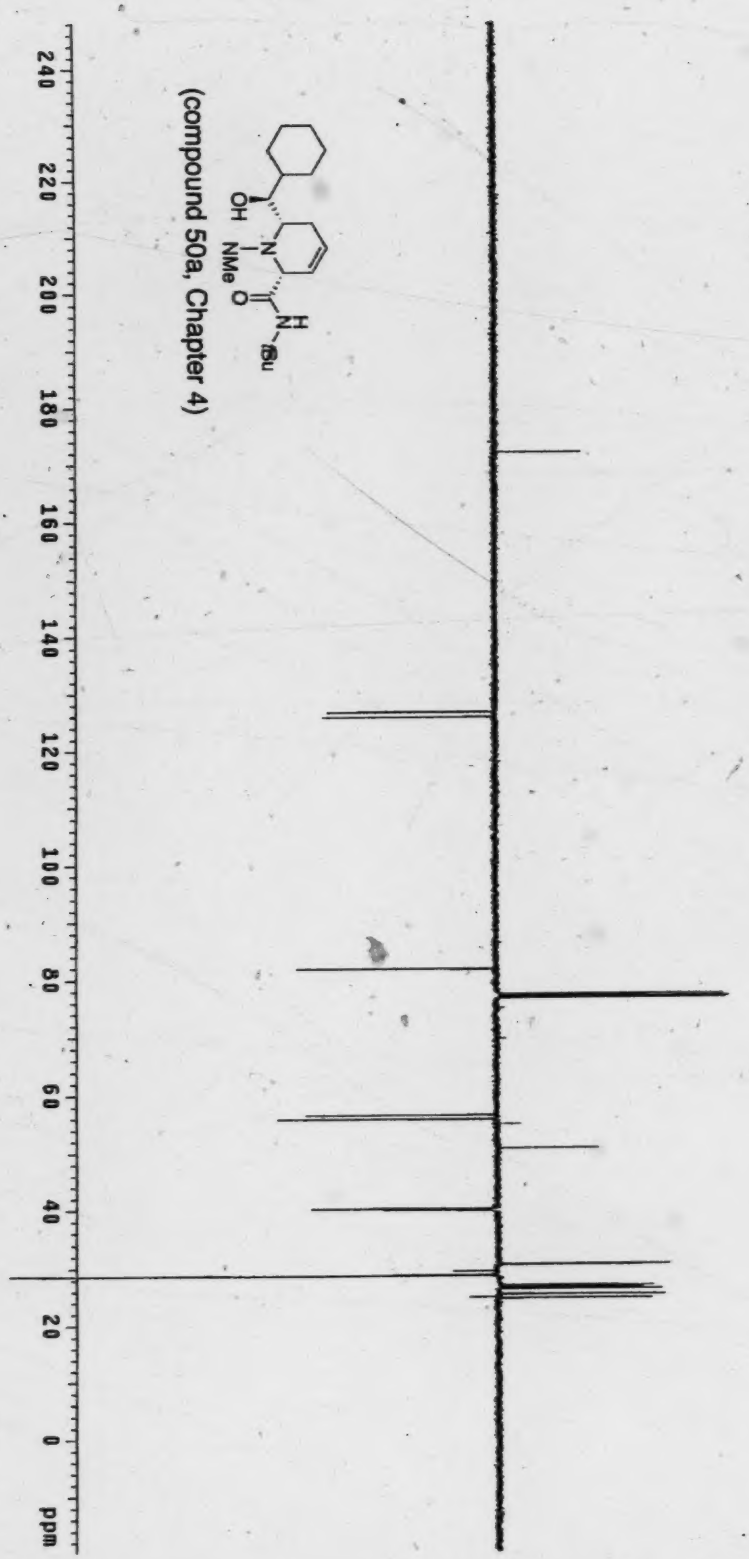
(compound 38, Chapter 5)



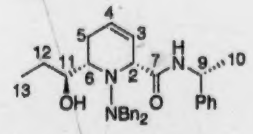
Appendix G

Representative ^{1}H NMR and APT spectra of the retro-sulfinyl-ene reaction products

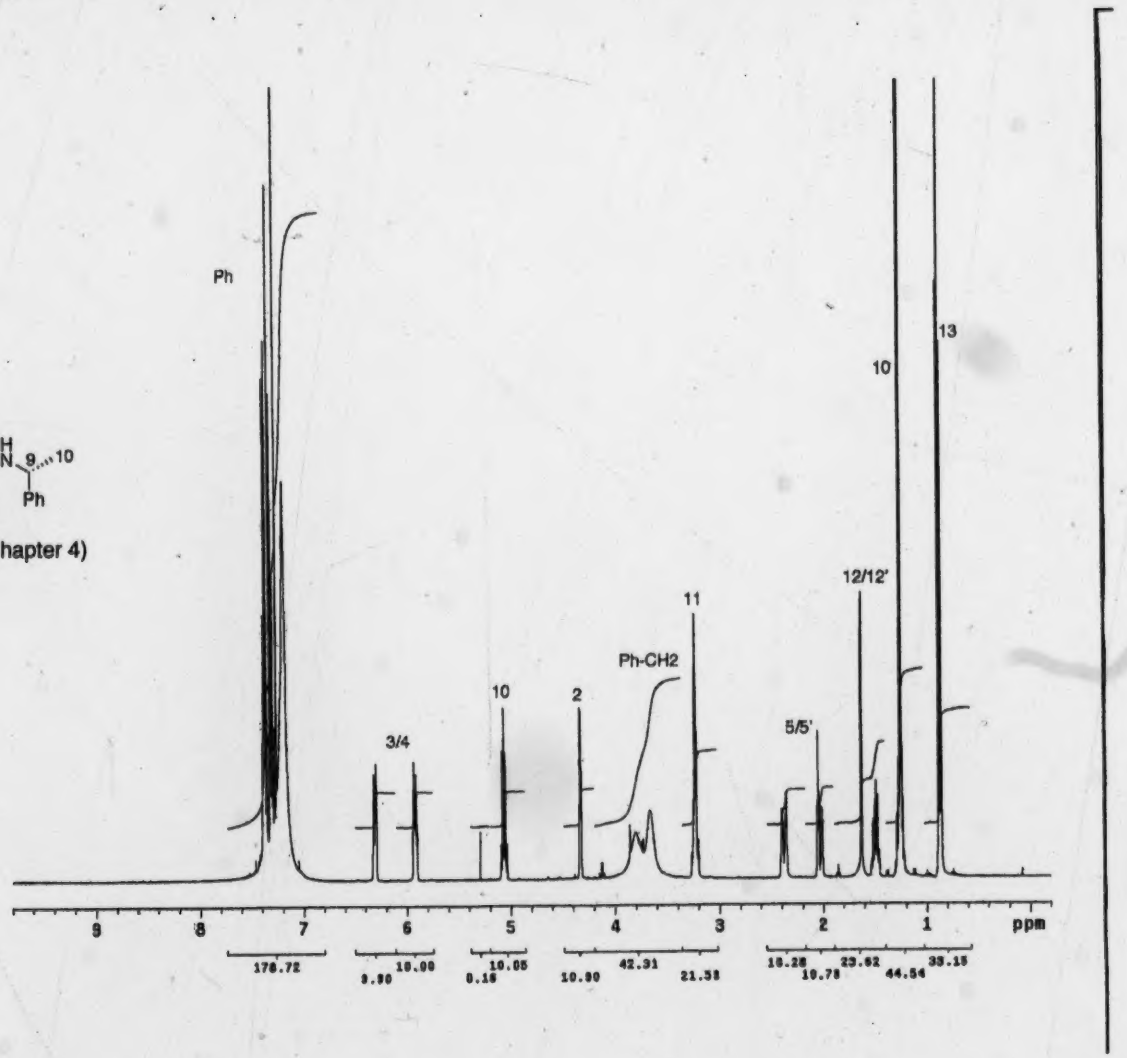


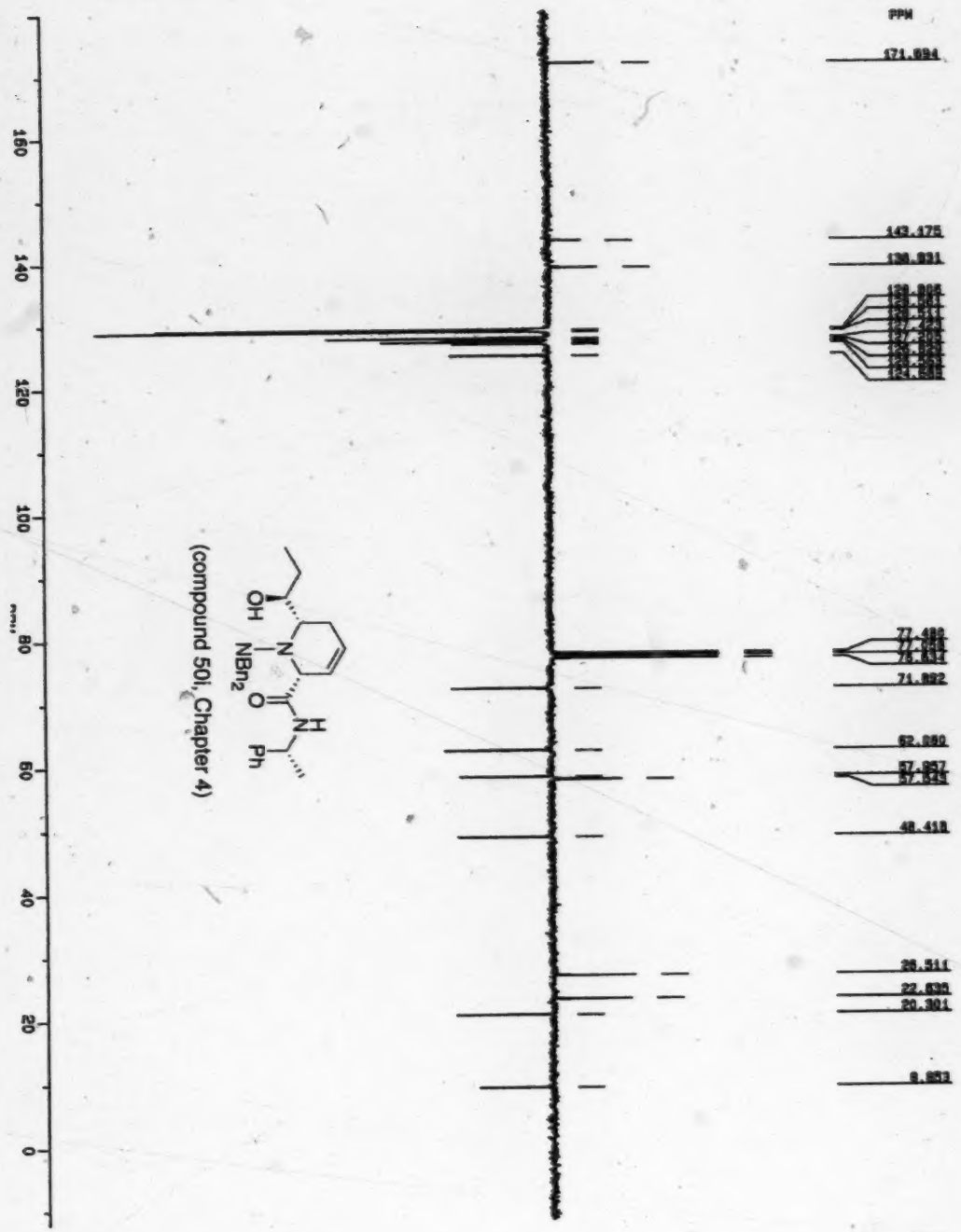


(compound 50a, Chapter 4)

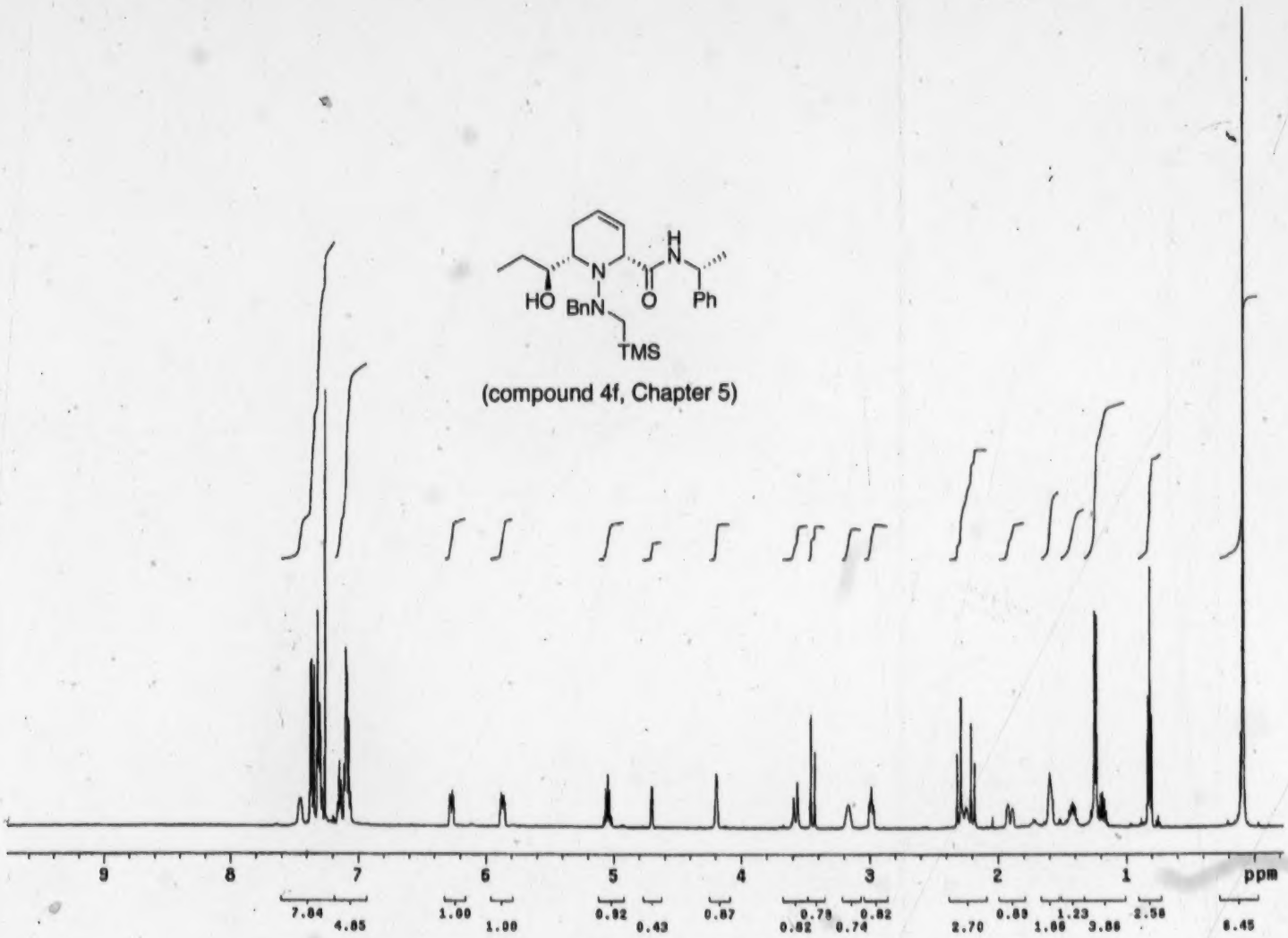


(compound 50i, Chapter 4)

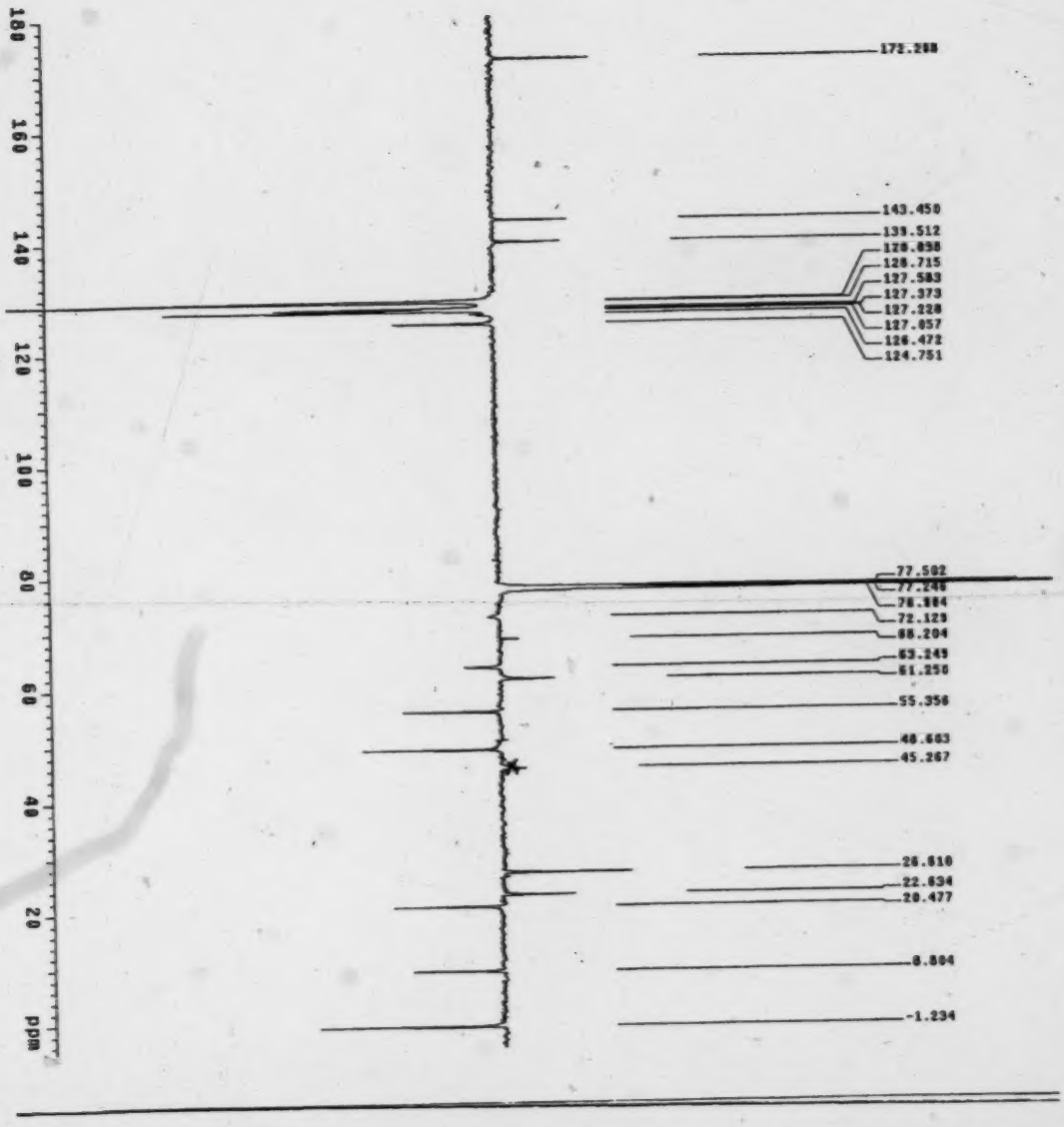




(compound 50i, Chapter 4)

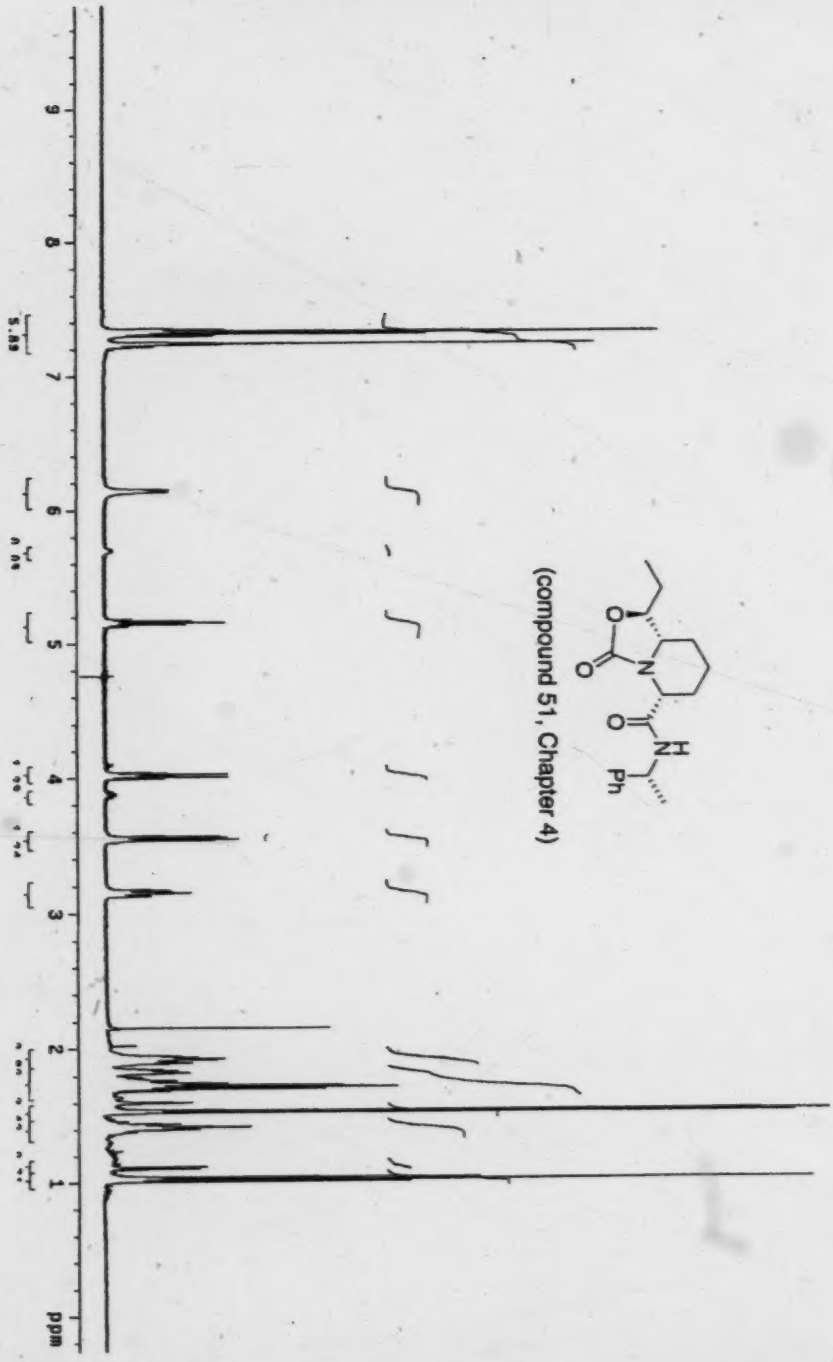


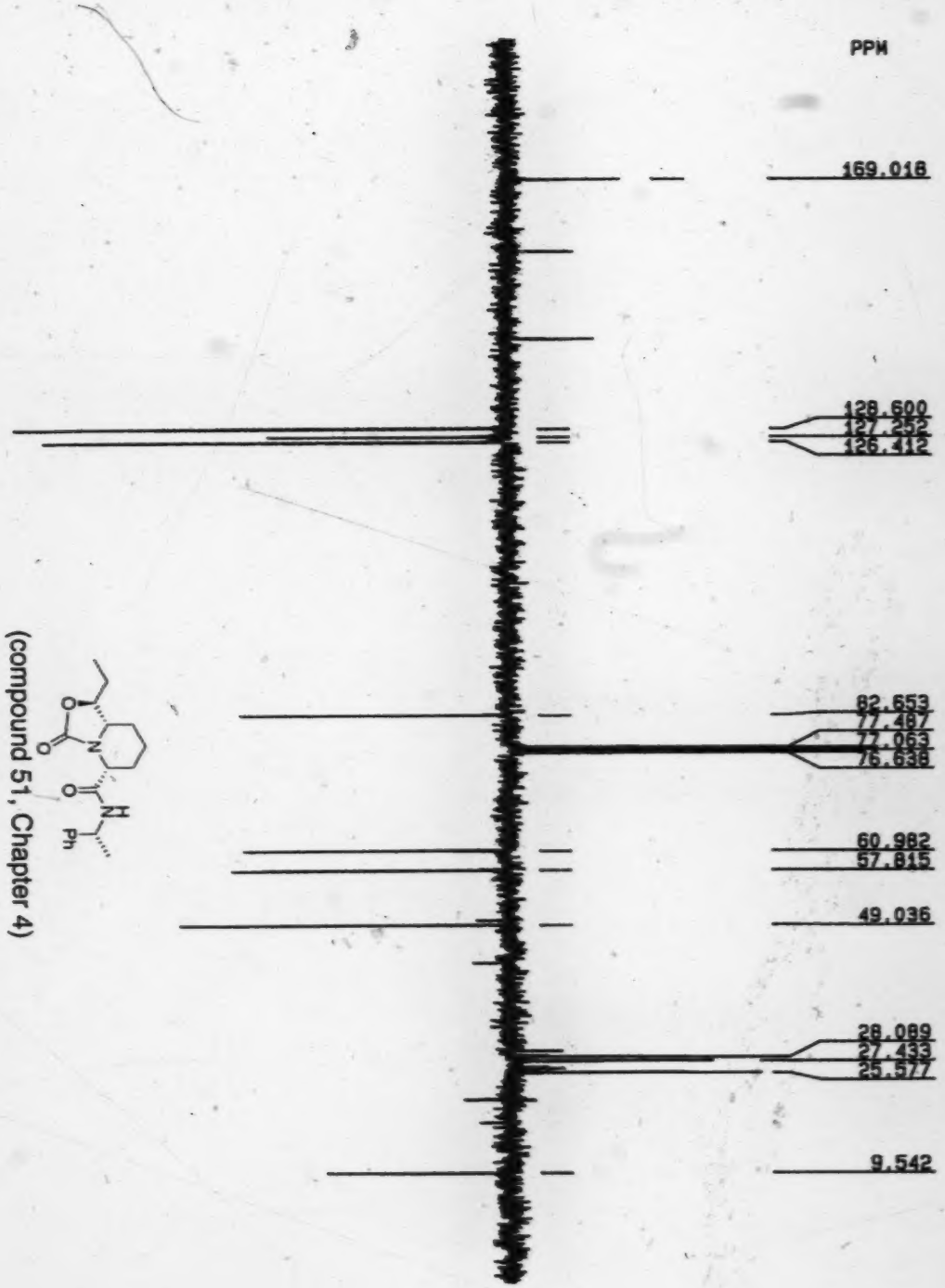
(compound 4f, Chapter 5)


(compound 4f, Chapter 5)
TMS
NBn
OH
O
N
H
Ph
172.288
143.450
139.512
128.838
128.715
127.583
127.373
127.228
127.057
126.472
124.751
77.502
77.248
76.994
72.129
68.204
63.249
61.250
55.356
48.663
45.267
26.810
22.634
20.477
8.804
-1.234
180
160
140
120
100
80
60
40
20
ppm

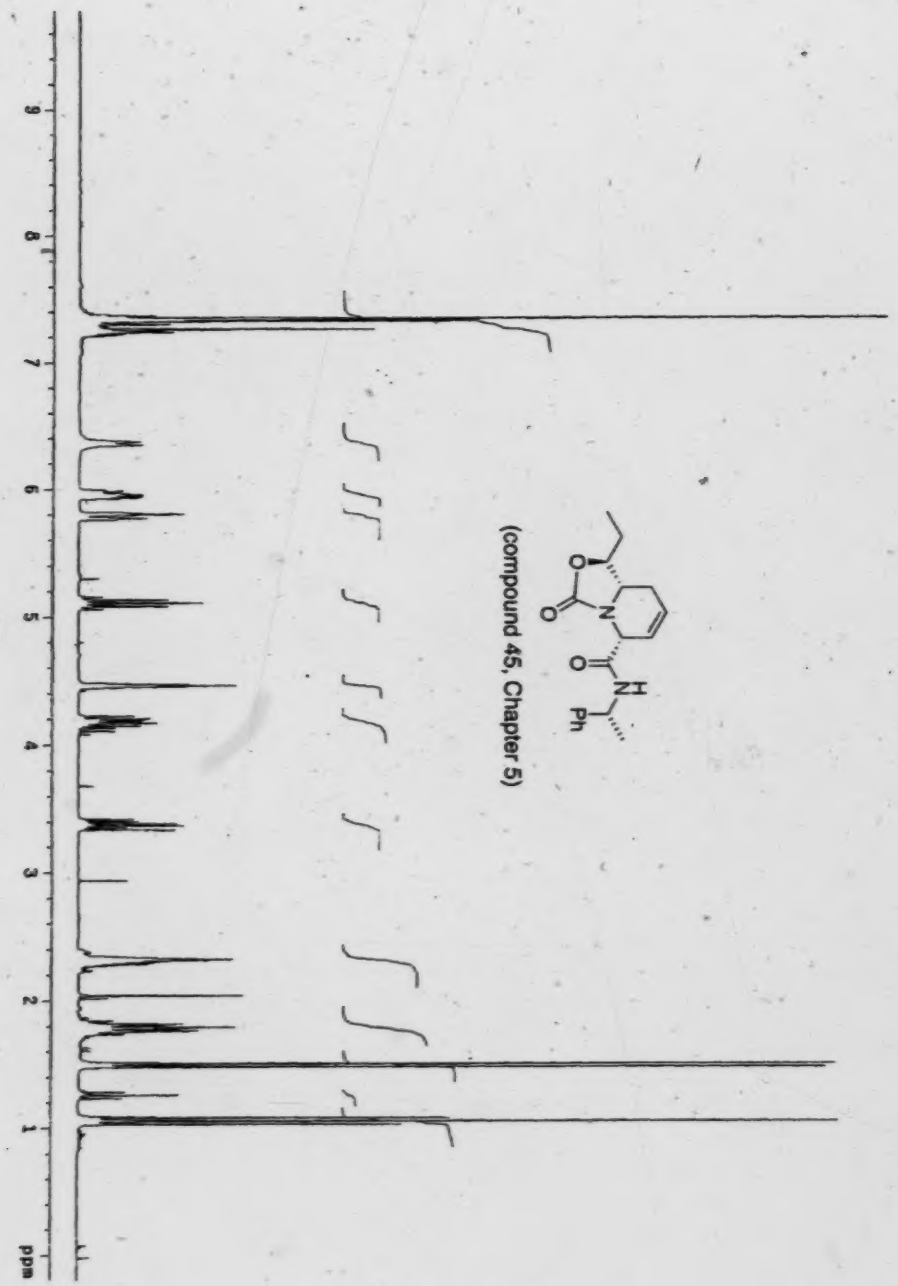
Appendix H

Representative ^{1}H NMR and APT spectra of important synthetic intermediates en route to the completed targets

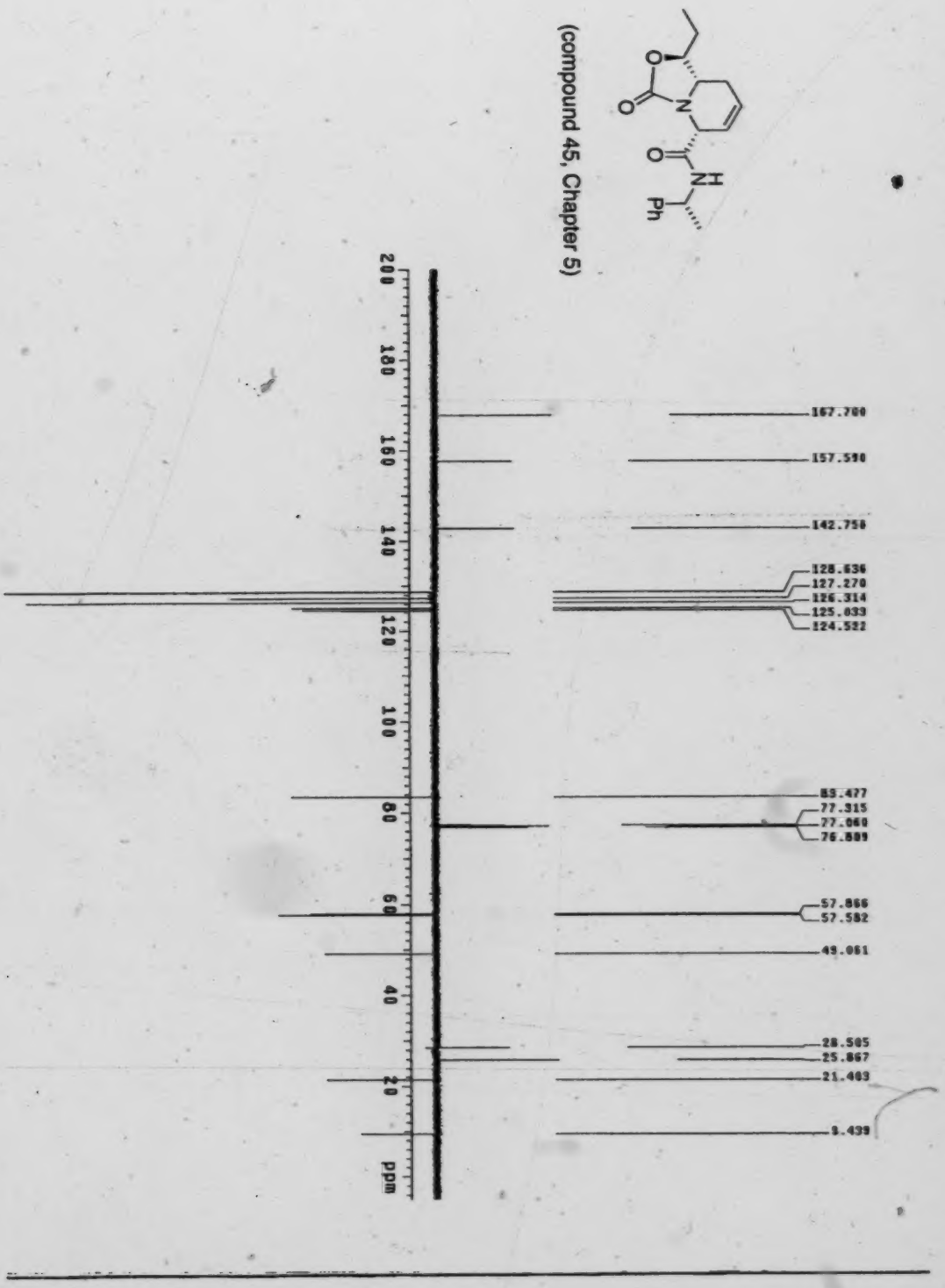


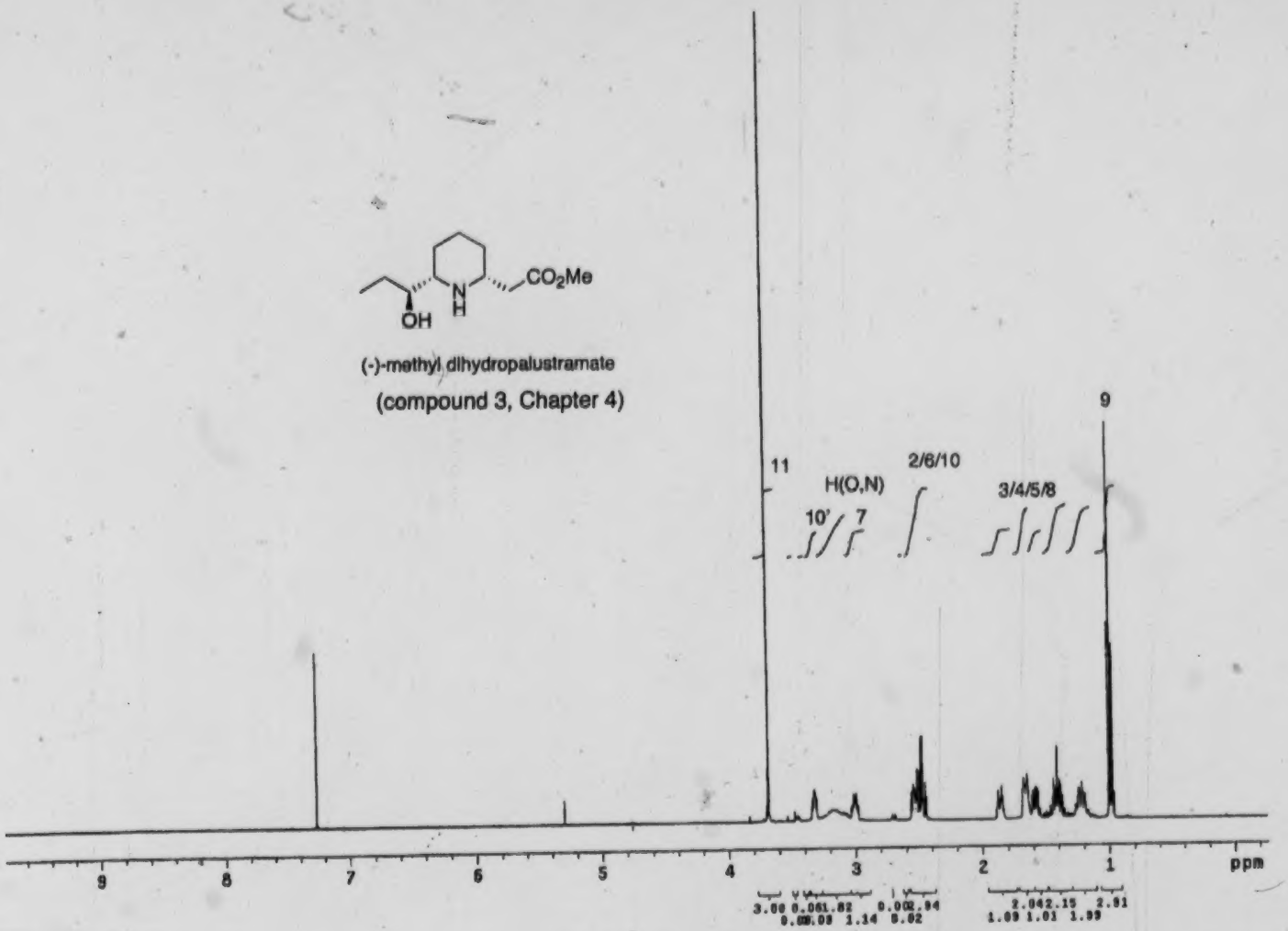


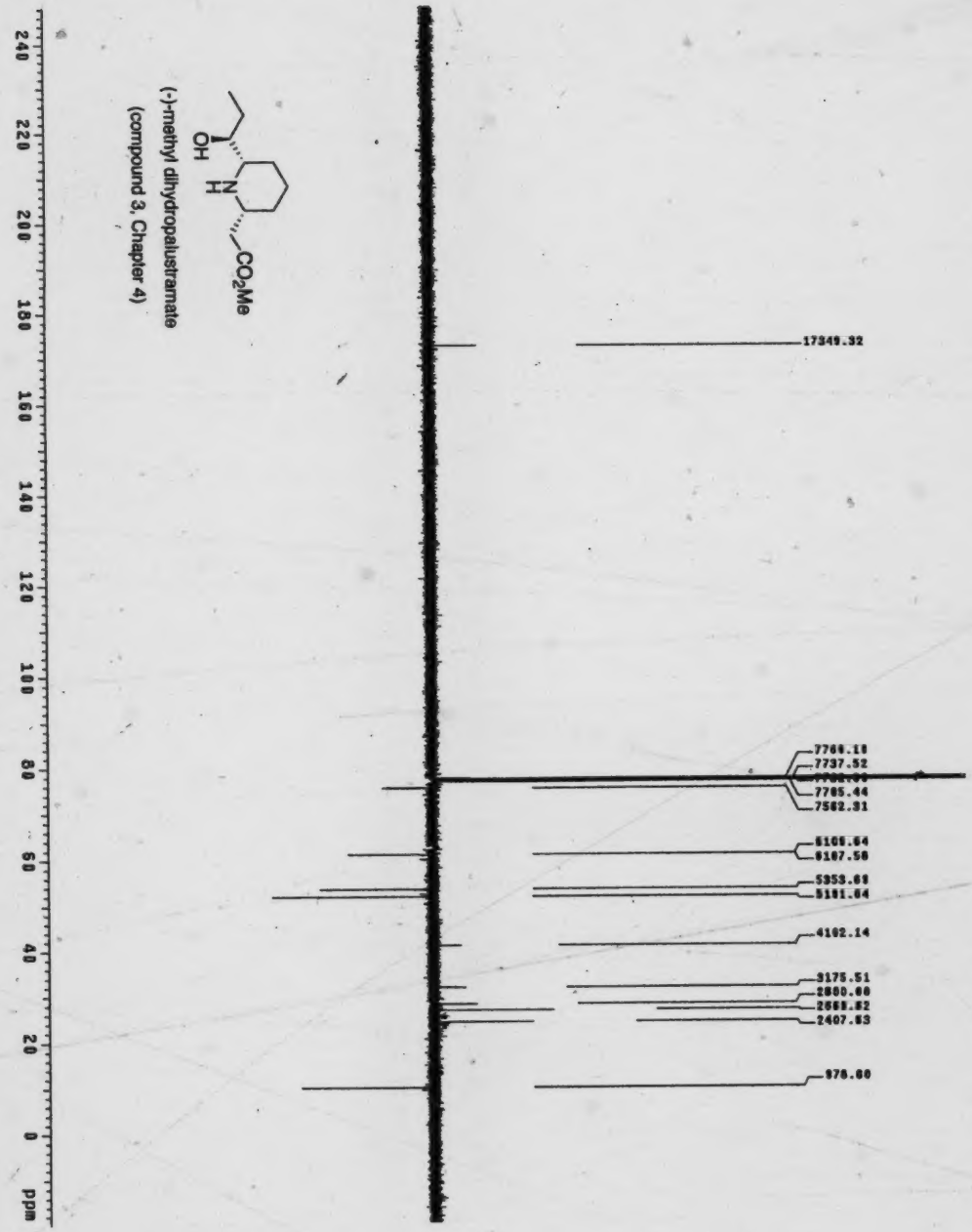
(compound 51, Chapter 4)

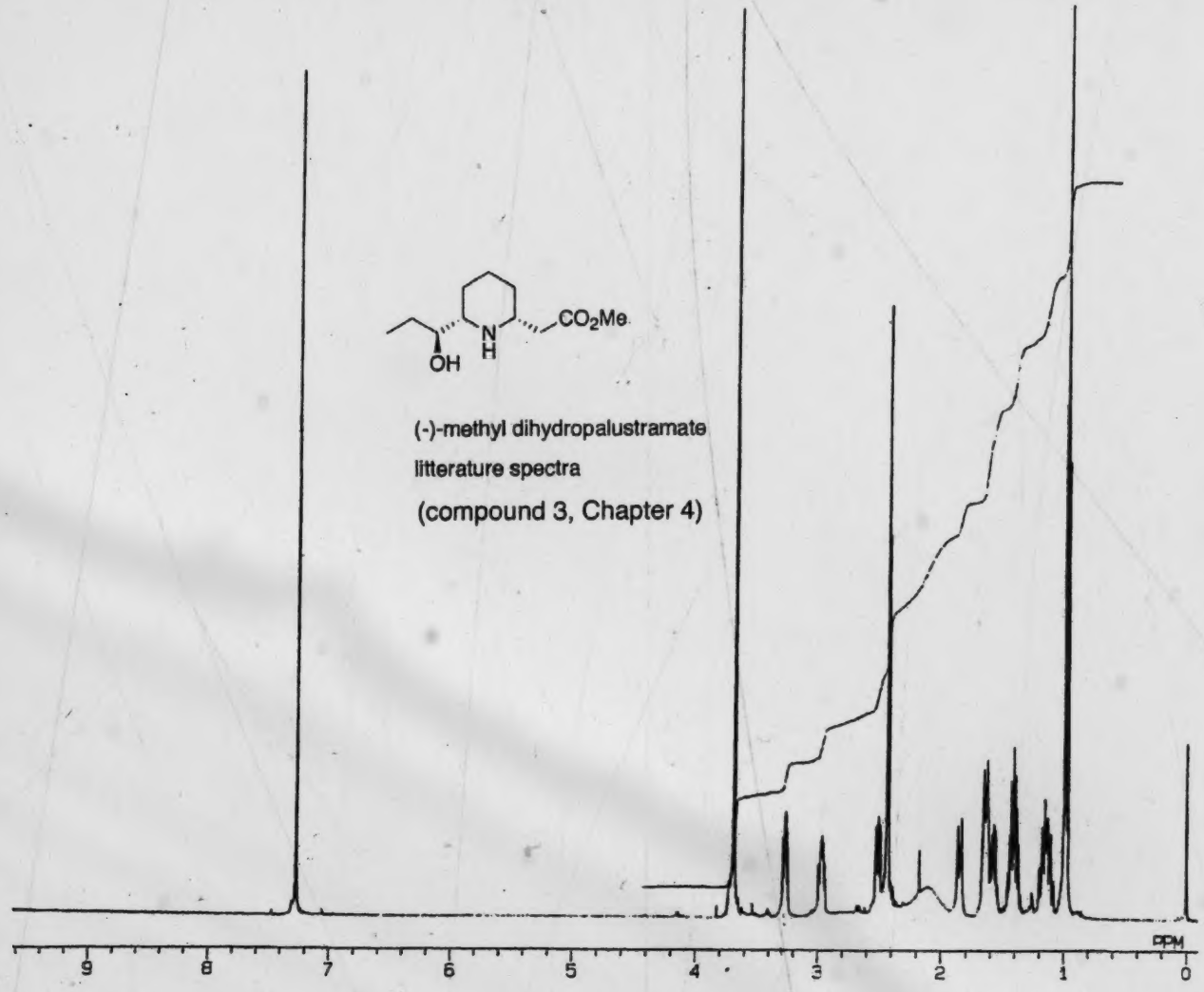

(compound 45, Chapter 5)
ppm

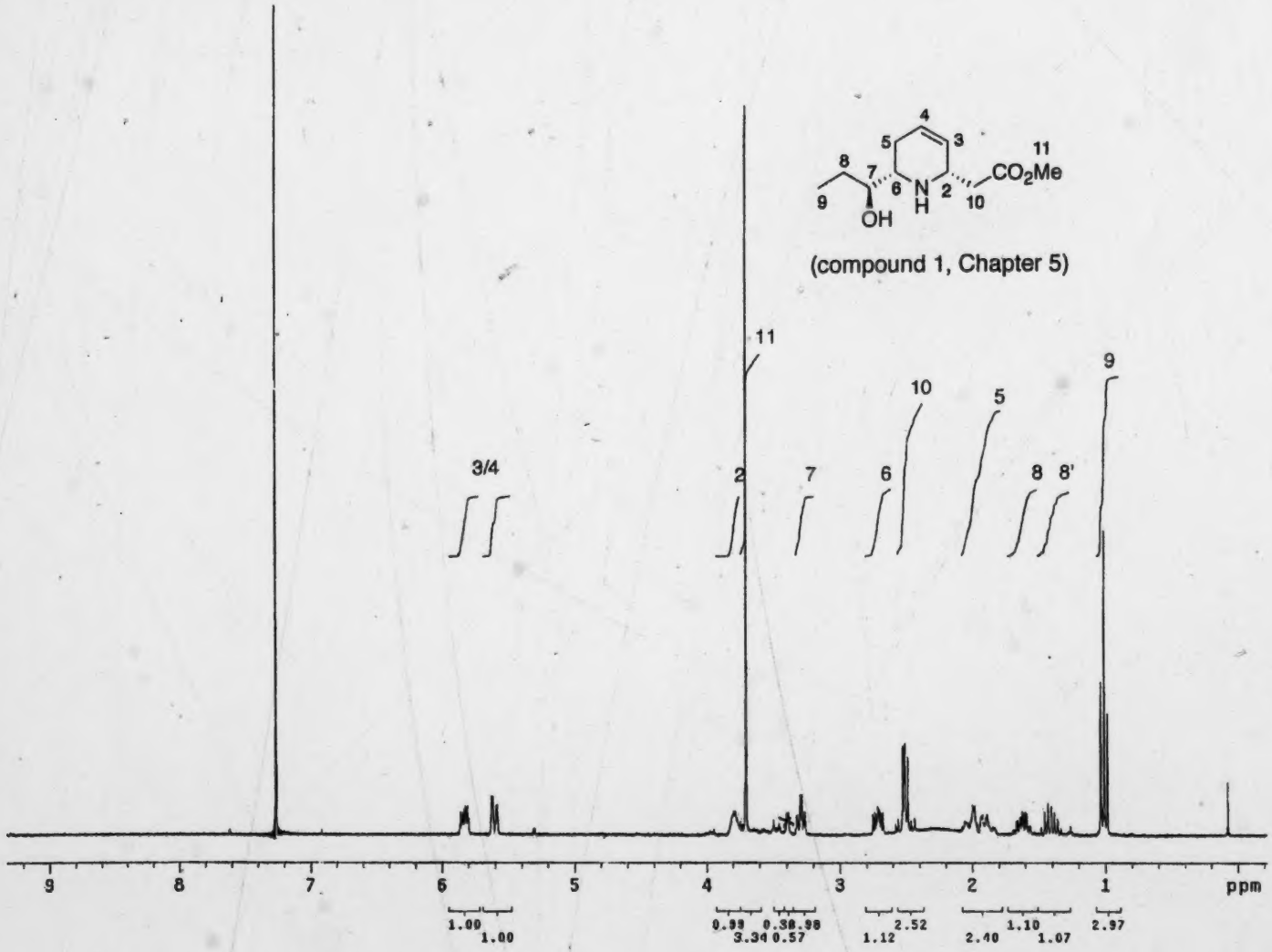
(compound 45, Chapter 5)

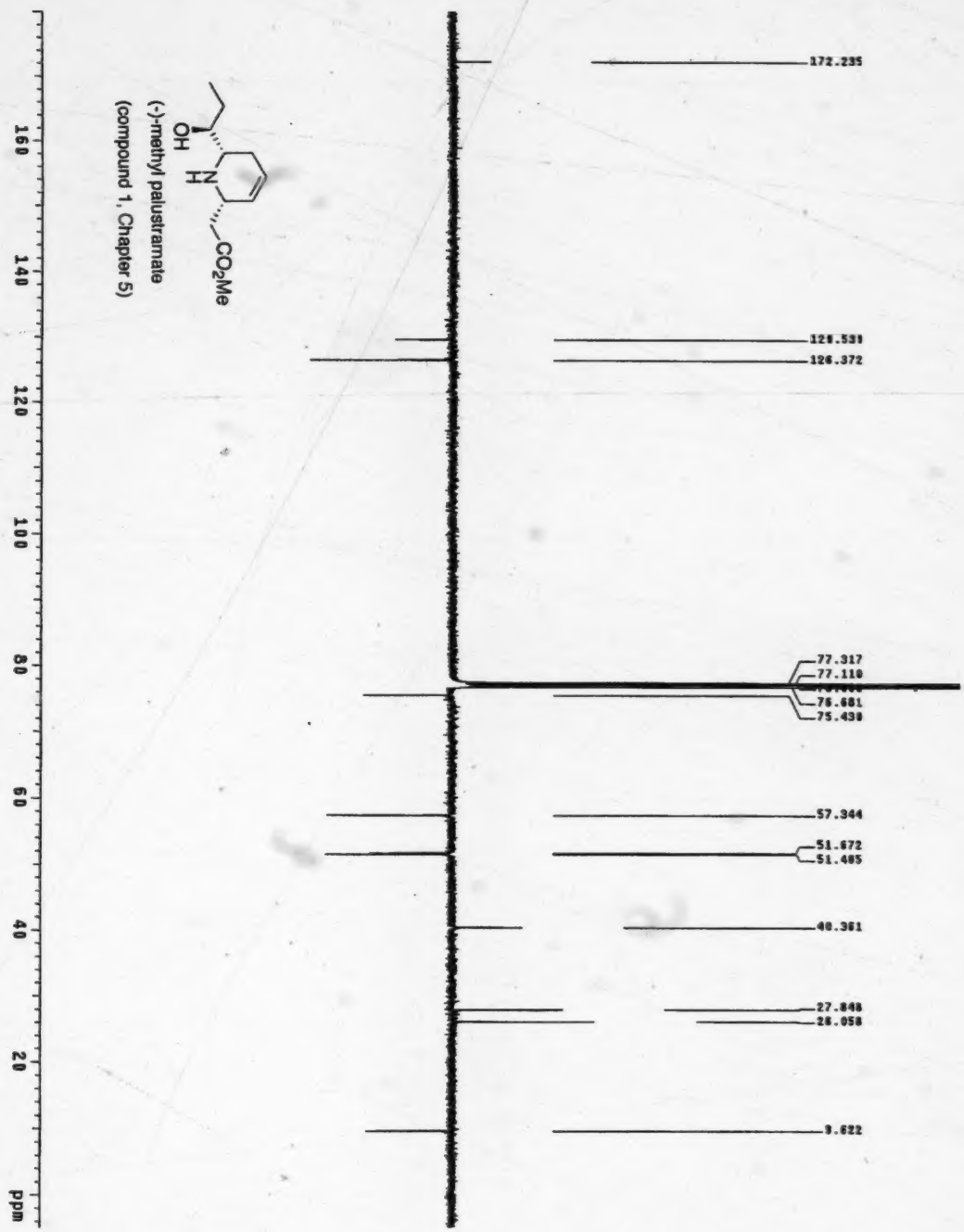


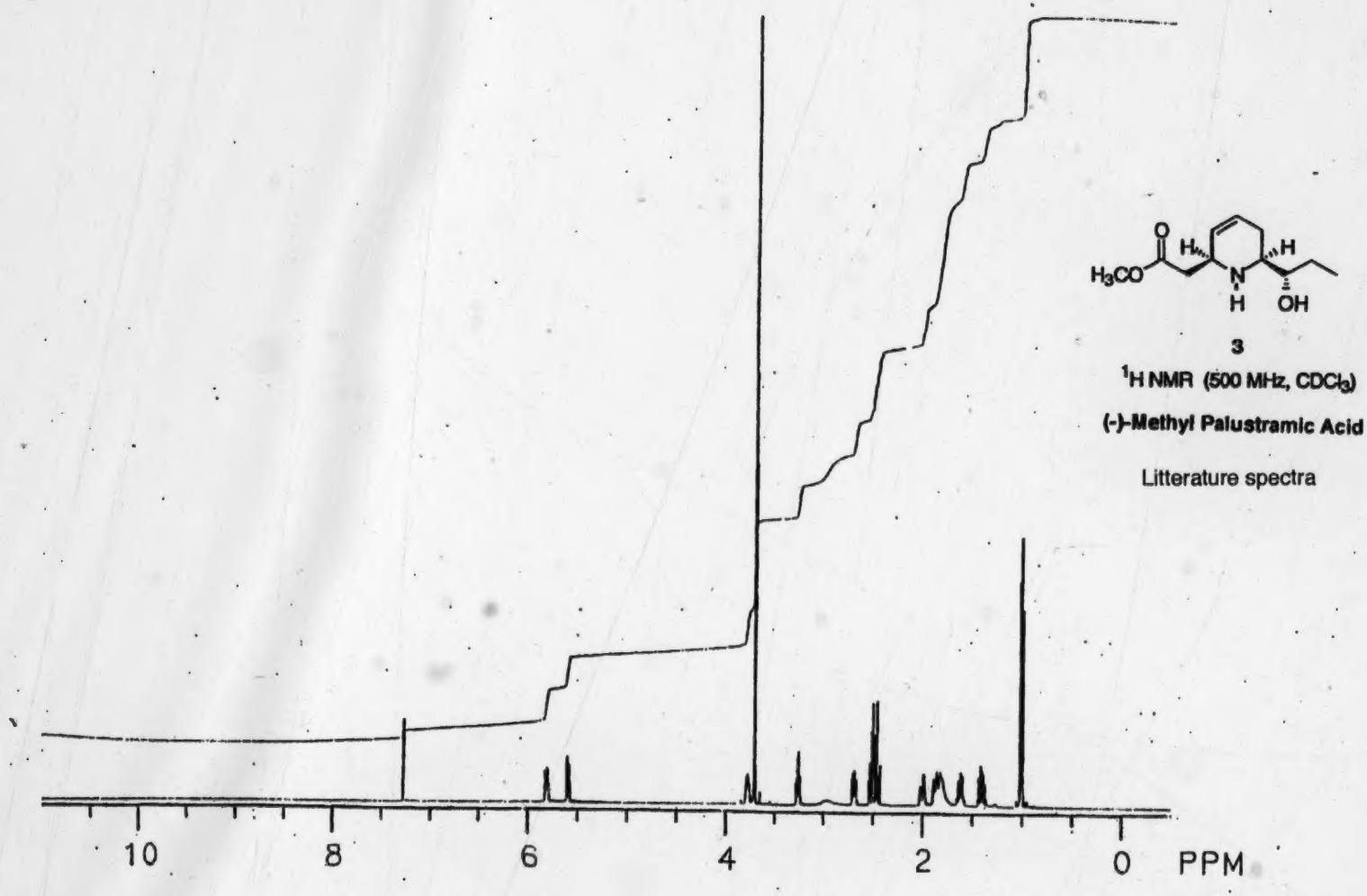

CO2Me
N
H
OH
(-)-methyl dihydropalustramate
(compound 3, Chapter 4)
11
H(O,N)
10'
7
2/6/10
3/4/5/8
9
9
8
7
6
5
4
3
2
1
ppm


OH
N
H
CO2Me
(-)-methyl dihydropalustramate
(compound 3, Chapter 4)
17349.32
7766.18
7737.52
7705.44
7562.31
6105.64
6107.58
5353.88
5181.84
4102.14
3175.51
2880.00
2688.82
2407.83
976.00
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm


CO2Me
N
H
OH
(-)-methyl dihydropalustramate
litterature spectra
(compound 3, Chapter 4)
9
8
7
6
5
4
3
2
1
0
PPM


4
5
3
11
8
7
CO2Me
9
6
N
H
2
10
OH
(compound 1, Chapter 5)
11
9
10
5
3/4
2
7
6
8
8'
9
8
7
6
5
4
3
2
1
ppm
1.00
1.00
0.98
3.34
0.38
0.57
0.98
1.12
2.52
2.40
1.10
1.07
2.97


(-)-methyl palustramate
(compound 1, Chapter 5)
OH
N
H
CO2Me
172.235
126.531
126.372
77.317
77.110
76.681
75.438
57.344
51.672
51.485
40.361
27.848
26.058
9.622
160
140
120
100
80
60
40
20
ppm



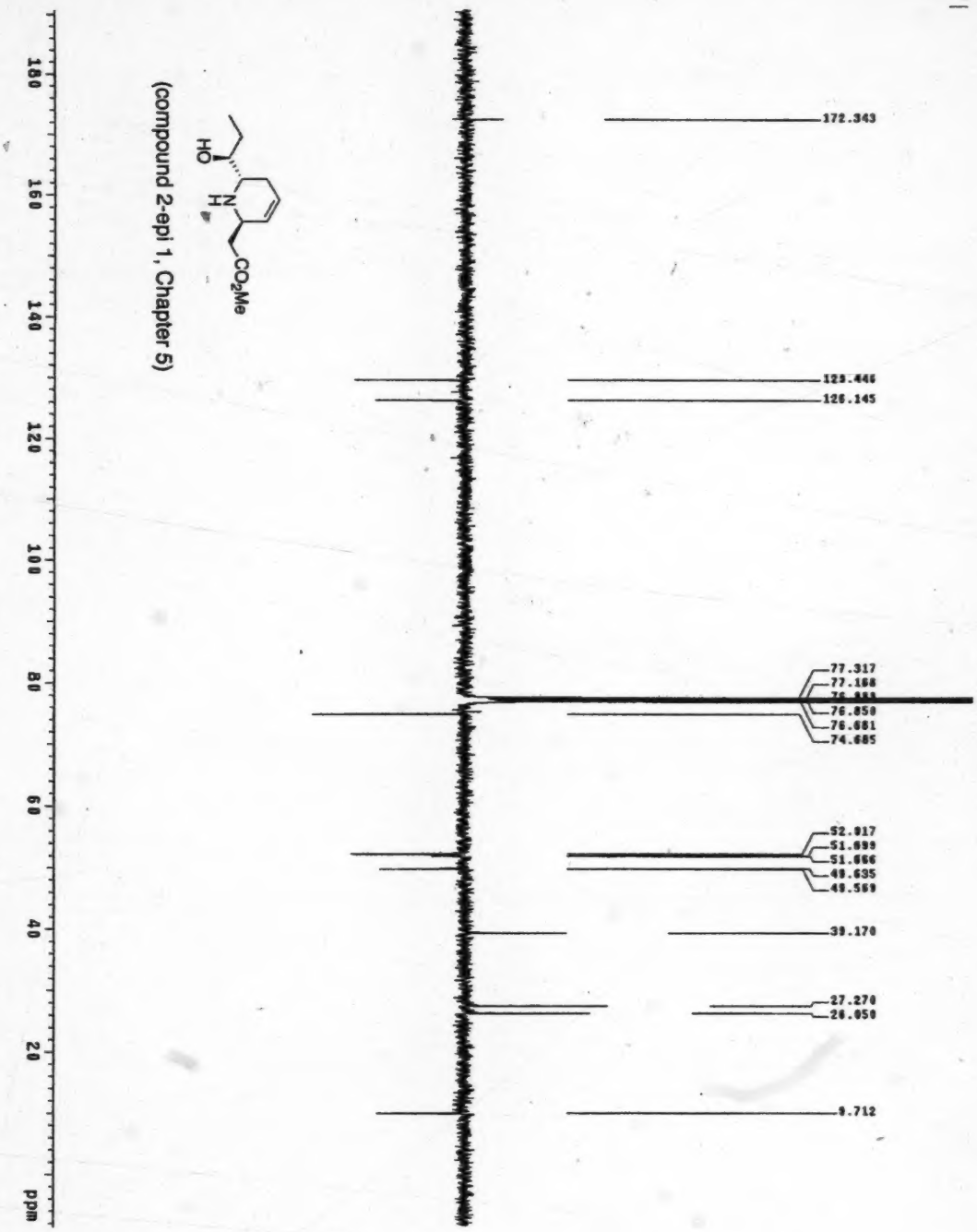
3

^{1}H NMR (500 MHz, $CDCl_3$)

(-)-Methyl Palustramic Acid

Litterature spectra

HO
N
H
CO2Me
(compound 2-epi 1, Chapter 5)
9
8
7
6
5
4
3
2
1
ppm



(compound 2-epi 1, Chapter 5)